



## AMENDED CLINICAL TRIAL PROTOCOL 02

**COMPOUND: Kevzara®/Sarilumab (SAR153191)**

**A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of sarilumab in patients with polymyalgia rheumatica**

**STUDY NUMBER: EFC15160**

---

Version Number:	1	EudraCT	2017-002989-42
		IND Number(s)	100632
		WHO universal trial number:	U1111-1201-0777
		Clinical trial.gov registration number:	NTC03600818
Date:	19-Apr-2021	Total number of pages:	138

---

Any and all information presented in this document shall be treated as confidential and shall remain the exclusive property of Sanofi (or any of its affiliated companies). The use of such confidential information must be restricted to the recipient for the agreed purpose and must not be disclosed, published or otherwise communicated to any unauthorized persons, for any reason, in any form whatsoever without the prior written consent of Sanofi (or the concerned affiliated company); 'affiliated company' means any corporation, partnership or other entity which at the date of communication or afterwards (i) controls directly or indirectly Sanofi, (ii) is directly or indirectly controlled by Sanofi, with 'control' meaning direct or indirect ownership of more than 50% of the capital stock or the voting rights in such corporation, partnership or other entity

## PROTOCOL AMENDMENT SUMMARY OF CHANGES

### DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02	All	Date: 19-Apr-2021, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01	All	Date: 19-Sep-2018, version 1 (electronic 1.0)
Clinical Trial Protocol		Date: 08-Feb-2018, version 1 (electronic 2.0)

### Amended protocol 02 (19 April 2021)

This amended protocol (amendment 02) is considered to be 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 significantly impacts the scientific value of the study.

### OVERALL RATIONALE FOR THE AMENDMENT

The overall rationale for the changes implemented in the protocol amendment is the inability to recruit due to COVID-19 resulting in premature termination of enrollment.

**Protocol amendment summary of changes table**

Section # and Name	Description of Change	Brief Rationale
Cover	Clinical trial.gov registration number "NTC03600818" added	
Section CLINICAL TRIAL SUMMARY-STUDY POPULATION- Total expected number of patients	Change in total expected number of patients	As a result of the inability to recruit due to the COVID19 pandemic, the study was terminated prematurely resulting in a change in the total expected number of patients.
Section CLINICAL TRIAL SUMMARY- STATISTICAL CONSIDERATIONS-Sample size determination	Change in statistical significance level from 0.01 to 0.05 and updated power	Due to the change in total expected number of patients, the statistical significance level has been changed and power calculations revised.
Section CLINICAL TRIAL SUMMARY- STATISTICAL CONSIDERATIONS-Primary analysis	Change significant level for analysis of primary efficacy endpoint from 0.01 to 0.05	Due to the change in total expected number of patients, the statistical significance level has been changed.

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
Section 6.5 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS	Change in total expected number of patients	As a result of the inability to recruit due to the COVID19 pandemic, the study was terminated prematurely resulting in a change in the total expected number of patients.
Section 11.1 Determination of sample size	Updated sample size and power calculations	Revised power calculations associated with the change in total expected sample size from 280 to 118, and the change in statistical significance level from 0.01 to 0.05.
Section 11.4.2.1 Analysis of primary efficacy endpoint(s)	Change significant level for analysis of primary efficacy endpoint from 0.01 to 0.05	Due to the change in total expected number of patients, the statistical significance level has been changed.
Section 11.4.2.2 Analysis of secondary efficacy endpoints	Revised 99% CI to 95% CI	Associated with the change in significant level from 0.01 to 0.05.
Section 11.4.2.3 Multiplicity considerations	Change significant level for analysis of secondary efficacy endpoints from 0.01 to 0.05	Due to the change in total expected number of patients, the statistical significance level has been changed.
Section 11.4.5 Analysis of patient reported outcomes	Revised 99% CI to 95% CI	Associated with the change in significant level from 0.01 to 0.05.
Section 17 Appendices	Addition of Appendix N: Protocol amendment history	

**NAMES AND ADDRESSES OF**

**COORDINATING  
INVESTIGATOR**

Name:  
Address:

Tel:  
Fax:  
E-mail:

**MONITORING TEAM'S  
REPRESENTATIVE**

Name:  
Address:

Tel:  
Fax:  
E-mail:

**SPONSOR**

Company:  
Address:

**OTHER EMERGENCY  
TELEPHONE NUMBERS**

## CLINICAL TRIAL SUMMARY

<b>COMPOUND: Sarilumab</b>	<b>STUDY No.: EFC15160</b>
<b>TITLE</b>	A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of sarilumab in patients with polymyalgia rheumatica (PMR).
<b>INVESTIGATOR/TRIAL LOCATION</b>	Worldwide
<b>PHASE OF DEVELOPMENT</b>	Phase 3
<b>STUDY OBJECTIVE(S)</b>	<p><b>Primary objective:</b></p> <ul style="list-style-type: none"> <li>To evaluate the efficacy of KEVZARA® (sarilumab) in patients with PMR as assessed by the proportion of subjects with sustained remission at Week 52 for sarilumab with a 14 weeks corticosteroid (CS) tapering regimen as compared to placebo with a 52 weeks CS tapering regimen.</li> </ul> <p><b>Secondary objective(s):</b></p> <ul style="list-style-type: none"> <li>To demonstrate the efficacy of sarilumab (with 14-week taper of CS) compared to placebo (with 52-weeks taper of CS) in patients with PMR with regard to: <ul style="list-style-type: none"> <li>Clinical responses (such as components of sustained remission, disease remission rates, time to first disease flare) over time.</li> <li>Cumulative corticosteroid (including prednisone) exposure.</li> </ul> </li> <li>To assess the safety (including immunogenicity) and tolerability of sarilumab in patients with PMR.</li> <li>To measure sarilumab concentrations from serum of patients with PMR.</li> <li>To assess the effect of sarilumab in reducing glucocorticoid toxicity as measured by the composite glucocorticoid toxicity index (GTI) questionnaire.</li> </ul> <p><b>Other objectives:</b></p> <ul style="list-style-type: none"> <li>To assess the effect of sarilumab on physician assessment of disease activity as measured by a visual analogue scale (MD-VAS).</li> <li>To assess the effect of sarilumab on a variety of PRO concepts, including fatigue (as measured by FACIT-fatigue scale), health status (as measured by EQ-5D-3L and SF-36v2), physical function (as measured by HAQ-DI), pain (as measured via HAQ-DI by a visual analogue scale [VAS]) and patient assessment of disease activity (as measured via HAQ-DI by a VAS).</li> <li>To assess the impact of ESR/CRP levels on remission status.</li> <li>To characterize the disease activity of PMR patients while on steroid taper or sarilumab treatment in a subset of patients using comprehensive approaches to evaluate</li> </ul>

	<p>circulating immune cell types.</p> <ul style="list-style-type: none"> <li>To characterize the disease activity of PMR patients while on steroid taper or sarilumab treatment by evaluating circulating proteins, genetics and gene expression in patients who consent for this optional part of the study.</li> </ul>
<p><b>STUDY DESIGN</b></p>	<p>This is a multicenter, randomized, double-blind, placebo-controlled 52-week study with a 6-week post-treatment follow-up phase, evaluating the efficacy and safety of sarilumab in patients with PMR. There are 2 parallel treatment groups with sarilumab 200 mg or placebo plus protocol defined CS tapering regimens of varying durations (as described below).</p> <p>Patients with active PMR will be randomized to the following 2 arms in a ratio of 1:1.</p> <ul style="list-style-type: none"> <li>Group 1: Sarilumab 200 mg once every 2 weeks (q2w) with a 14 week taper of CS.</li> <li>Group 2: Sarilumab matching placebo q2w with a 52 week taper of CS.</li> </ul> <p>All patients will receive sarilumab 200 mg or placebo for 52 weeks. Upon randomization at baseline, patients will start the protocol defined taper of prednisone of either 14 weeks duration or 52 weeks duration. All patients will receive prednisone 15 mg/day during the initial 2 weeks of the taper.</p> <p>During the initial 12 weeks of prednisone taper, treatment for one flare before Week 12 is permitted if it can be successfully treated with a low dose (<math>\leq 5</math> mg/day) prednisone add-on taper regimen (completed prior to Week 12) and provided that all other sustained remission parameters are met.</p> <p>For the management of predefined neutropenia, thrombocytopenia and alanine aminotransferase increases, study drug (sarilumab/matching placebo) must be temporarily withheld and a request to reduced dosage to sarilumab 150 mg q2w (for patients randomized to the 200 mg q2w arm only)/matching placebo may be made in a blinded manner through IRT system which will implement the request appropriately based upon the patient's treatment assignment, based on investigator judgment.</p> <p>Patients, who experience a flare or persistent disease activity and cannot follow the per protocol CS taper during the 52-week treatment period or the permitted prednisone add-on treatment prior to Week 12, will continue in the study with a CS rescue regimen as determined by the Investigator (as long as it does not pose a safety risk or contraindication with concomitant sarilumab administration) while double-blind injections of sarilumab or matching placebo will continue for the full 52 week treatment period.</p> <p>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 evaluation.</p>

<p><b>STUDY POPULATION</b></p> <p><b>Main selection criteria</b></p>	<p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"><li>• Diagnosis of PMR according to the European League against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria as follows (must satisfy all criteria):<ul style="list-style-type: none"><li>- Age <math>\geq</math>50 years at time of diagnosis.</li><li>- Bilateral shoulder pain.</li><li>- Elevated acute phase reactants CRP &gt;10 mg/L and/or ESR &gt;30 mm/hour.</li></ul></li></ul> <p>AND one of the following:</p> <ul style="list-style-type: none"><li>- A score <math>\geq</math>4 at the time of diagnosis based on the following (without ultrasound):<ul style="list-style-type: none"><li>- Duration of morning stiffness &gt;45 minutes: 2 points</li><li>- Hip pain or limited range of motion: 1 point.</li><li>- Seronegative for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP): 2 points.</li><li>- Absence of other joint involvement: 1 point.</li></ul></li></ul> <p>OR</p> <ul style="list-style-type: none"><li>- A score <math>\geq</math>5 at the time of diagnosis based on the following (with ultrasound):<ul style="list-style-type: none"><li>- Duration of morning stiffness &gt;45 minutes: 2 points.</li><li>- Hip pain or limited range of motion: 1 point.</li><li>- Seronegative for RF and anti-CCP: 2 points.</li><li>- Absence of other joint involvement: 1 point.</li><li>- At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either Posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis: 1 point. (confirmed with ultrasound)</li><li>- Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis: 1 point. (confirmed with ultrasound)</li></ul></li></ul> <ul style="list-style-type: none"><li>• Patients must be on prednisone of at least 7.5 mg/day (or equivalent) and not exceeding 20 mg/day at screening and during the screening period.</li><li>• Patient is willing and able to take prednisone of 15 mg/day at randomization.</li><li>• Patients must have a history of being treated for at least 8 weeks with prednisone (<math>\geq</math>10 mg/day or equivalent).</li><li>• Patient must have had at least one episode of unequivocal PMR flare while attempting to taper prednisone at a dose that is <math>\geq</math>7.5 mg/day (or equivalent) within the past 12 Weeks prior to screening:<ul style="list-style-type: none"><li>- Unequivocal symptoms of PMR flare include shoulder and/or hip girdle pain associated with inflammatory stiffness.</li></ul></li><li>• Patients must have ESR <math>\geq</math>30 mm/hr and/or CRP <math>\geq</math>10 mg/L associated with PMR disease activity within 12 weeks prior to screening.</li></ul>
--	---

	<p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Diagnosis of giant cell arteritis (GCA) (eg, persistent or recurrent localized headache, temporal artery or scalp tenderness, jaw claudication, extremity claudication, blurry or loss of vision, symptoms of stroke).</li> <li>• Concurrent diagnosis of active fibromyalgia.</li> <li>• Concurrent rheumatoid arthritis or other inflammatory arthritis or other connective tissue diseases, such as but not limited to systemic lupus erythematosus, systemic sclerosis, vasculitis, myositis, mixed connective tissue disease, and ankylosing spondylitis.</li> <li>• Concurrent diagnosis of rhabdomyolysis or neuropathic muscular diseases.</li> <li>• Inadequately treated hypothyroidism.</li> <li>• Organ transplant recipient.</li> <li>• Therapeutic failure including inadequate response or intolerance, or contraindication, to biological IL-6 antagonist.</li> <li>• Any prior (within the defined washout period below) or concurrent use of immunosuppressive therapies but not limited to any of the following:             <ul style="list-style-type: none"> <li>- Janus kinase (JAK) inhibitor within 4 weeks of baseline.</li> <li>- Alkylating agents including cyclophosphamide within 6 months of baseline.</li> <li>- Cell-depletion agents (eg, anti CD20) without evidence of recovery of B cells to baseline level.</li> <li>- Tumor necrosis factor (TNF) inhibitors within 2-8 weeks (etanercept within 2 weeks, infliximab, certolizumab, golimumab, or adalimumab within 8 weeks), or after at least 5 half-lives have elapsed, whichever is longer.</li> <li>- Abatacept within 8 weeks of baseline.</li> <li>- Anakinra within 1 week of baseline.</li> <li>- Cyclosporine (CsA), azathioprine (AZA) or mycophenolate mofetil (MMF) or leflunomide within 4 weeks of baseline.</li> </ul> </li> <li>• Unstable methotrexate (MTX) dose and/or MTX dose &gt;15 mg/week within 3 months of baseline</li> <li>• Concurrent use of systemic CS for conditions other than PMR.</li> <li>• Evidence of serious, uncontrolled concomitant disease (eg, cardiovascular, respiratory, hepatic, renal, endocrine etc.).</li> </ul>
<p><b>Total expected number of patients</b></p>	<p>Approximately 280 revised to 118</p>



STUDY TREATMENT(s)	
<p><b>Investigational medicinal product</b></p> <p><b>Formulation:</b></p> <p><b>Route(s) of administration:</b></p> <p><b>Dose regimen:</b></p>	<p>Sarilumab</p> <p>Single-use prefilled glass syringes of sarilumab 200 mg, sarilumab 150 mg or matching placebo for sarilumab.</p> <p>Subcutaneous (SC) route, in abdomen or thigh, or upper arm.</p> <p>Sarilumab 200 mg, sarilumab 150 mg or matching placebo is to be administered q2w.</p>
<p><b>Investigational medicinal product</b></p> <p><b>Formulation:</b></p> <p><b>Route(s) of administration:</b></p> <p><b>Dose regimen:</b></p>	<p>Prednisone and matching placebo will be used in the study for standardized prednisone-taper regimen for treatment of PMR.</p> <p>Phase 1: 5 mg over-encapsulated tablets, Phase 2: over-encapsulated matching placebo tablets</p> <p>Oral administration</p> <p>For the purpose of this study, there will be 2 standardized CS-taper regimens:</p> <ul style="list-style-type: none"> <li>• 14 weeks - initial 2 weeks of 15mg/day dose followed by 12 weeks of gradual decrease in dose (sarilumab treatment arm).</li> <li>• 52 weeks - initial 2 weeks of 15mg/day dose followed by 50 weeks of gradual decrease in dose (sarilumab matching placebo treatment arm).</li> </ul> <p>Blinding of CS treatment:</p> <ul style="list-style-type: none"> <li>• Prednisone and matching placebo will be used to maintain blinding of the taper regimen.</li> </ul>
<p><b>Investigational medicinal product</b></p> <p><b>Formulation:</b></p> <p><b>Route(s) of administration:</b></p> <p><b>Dose regimen:</b></p>	<p>Add-on Prednisone</p> <p>Add on ≤5 mg regimen: Commercial 1 mg tablets</p> <p>Oral administration</p> <p>As determined by the investigator but up to maximum dose of 5mg/day</p>
<p><b>Non-Investigational medicinal product</b></p> <p><b>Formulation:</b></p> <p><b>Route(s) of administration:</b></p>	<p>Rescue corticosteroids</p> <p>Commercial tablets</p> <p>Oral administration</p>
<p><b>Dose regimen:</b></p>	<p>As determined by the investigator</p>

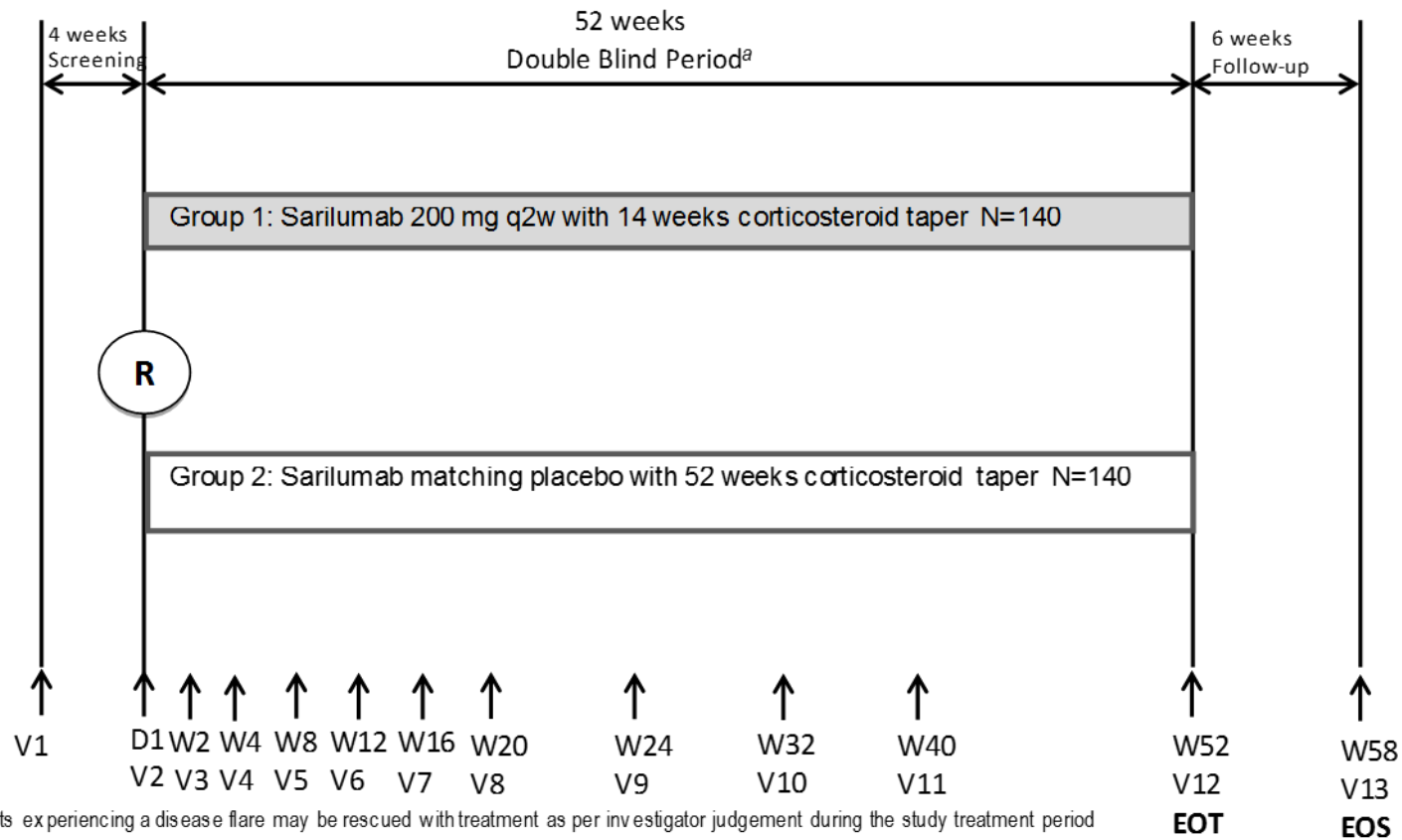
<p><b>ENDPOINT(S)</b></p>	<p><b>Primary endpoint:</b></p> <p>Proportion of patients achieving sustained remission at Week 52. Sustained remission at Week 52 is defined by having met all of the following parameters:</p> <ul style="list-style-type: none"> <li>• Achievement of disease remission no later than Week 12, AND</li> <li>• Absence of disease flare from Week 12 through Week 52, AND</li> <li>• Sustained reduction of CRP (to &lt;10 mg/L, with an absence of successive elevations to ≥10 mg/L) from Week 12 through Week 52, AND</li> <li>• Successful adherence to the prednisone taper from Week 12 through Week 52.</li> </ul> <p><b>Disease remission</b> is defined as resolution of signs and symptoms of PMR, and normalization of CRP (&lt;10 mg/L).</p> <p>Note: A single CRP elevation (≥10 mg/L) is not considered absence of remission unless CRP remains elevated (≥10 mg/L) at 2 consecutive study visits.</p> <p><b>Flare</b> is defined as recurrence of signs and symptoms attributable to active PMR requiring an increase in CS dose, or elevation of ESR attributable to active PMR plus an increase in CS dose. Increase in CS dose is defined as:</p> <ul style="list-style-type: none"> <li>• Any dose increase during the protocol defined steroid taper.</li> <li>• Re-initiation of prednisone therapy after the protocol defined taper has been completed.</li> </ul> <p><i>Note: During the initial 12 weeks of prednisone taper, treatment for one flare before Week 12 is permitted if it can be successfully treated with a ≤5 mg/day prednisone add-on taper regimen (completed prior to Week 12) and provided that all other sustained remission parameters are met.</i></p> <p><b>Secondary endpoint(s):</b></p> <p><b>Efficacy:</b></p> <ul style="list-style-type: none"> <li>• Summary of the components of sustained remission at Week 52.</li> <li>• Total cumulative prednisone dose (or equivalent) over 52 weeks.</li> <li>• Time to first PMR flare</li> <li>• Changes from baseline in GTI (and components)</li> </ul> <p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>• Adverse events (AEs), laboratory values (including antidrug antibody [ADA], vital signs).</li> </ul> <p><b>Pharmacokinetic</b></p> <ul style="list-style-type: none"> <li>• Serum concentrations of sarilumab.</li> </ul> <p><b>Other efficacy endpoint(s):</b></p> <ul style="list-style-type: none"> <li>• Change from baseline in the Physician global assessment of disease activity- visual analog scale (MD-VAS).</li> </ul>
---------------------------	--

	<ul style="list-style-type: none"> <li>• Patient Reported Outcome (changes from baseline for the following):             <ul style="list-style-type: none"> <li>- Functional assessment of chronic illness therapy fatigue scale (FACIT-fatigue) – total score.</li> <li>- EuroQol 5 dimension questionnaire; 3-level version (EQ-5D-3L) – index score and visual analogue scale score.</li> <li>- Short-form 36-item questionnaire (SF-36v2) – domain scores, and physical and mental component summary scores</li> <li>- Health Assessment Questionnaire Disability Index (HAQ-DI) – total score, pain score, patient global impression score</li> </ul> </li> </ul> <p><b>Pharmacodynamic</b></p> <ul style="list-style-type: none"> <li>• Changes in ESR and CRP over time.</li> <li>• Changes in IL-6 level and soluble IL-6 receptor.</li> <li>• Changes in markers of inflammation and disease activity over time as assessed in circulating immune cell types, circulating proteins and gene expression changes.</li> </ul>
<p><b>ASSESSMENT SCHEDULE</b></p>	<p>The study will consist of the following visits:</p> <ul style="list-style-type: none"> <li>• Visit 1 (D-28-D-1): Screening</li> <li>• Visit 2 (D1): Baseline, randomization, first study drug administration.</li> <li>• Visit 3 to 11 (Week 2-Week 40): on treatment (during double-blind phase).</li> <li>• Visit 12 (Week 52): End of Treatment (EOT) visit (last SC IMP administration at Week 50 and last oral IMP administration day before Visit 12).</li> <li>• Visit 13 (Week 58): End of Study (EOS) visit.</li> </ul> <p>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.</p> <p>For an overview of the laboratory tests see the study flow chart below, which 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. Future Use Sample (serum and plasma) used for future analysis (eg, circulating proteins) will be collected from each consenting patient using a separate informed consent form (optional). Blood samples (DNA and RNA for sequencing or gene expression [RNA only]) will be collected from each consenting patient using a separate informed consent form (optional).</p> <p>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</p>

	<p>permanent discontinuation and TB, and potential opportunistic infections.</p> <p>A dual assessor approach will be required in order to maintain the blind during the double-blind treatment period with sarilumab, prednisone and matching placebos. The Efficacy Assessor should be a rheumatologist or other skilled PMR assessor and may be the principal investigator who will be responsible for completing the overall evaluation and management of PMR disease activity. The Safety Assessor should be a physician who will be responsible for assessing and managing any safety concerns related to the patient during the course of the study including reviewing the patient's laboratory data and assessing/reporting/managing any AEs. The Safety Assessor cannot be the Efficacy Assessor.</p> <p>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.</p> <p>Blood samples in a subset of patients will be collected to evaluate circulating immune cell phenotypes.</p>
<p><b>STATISTICAL CONSIDERATIONS</b></p>	<p><b>Sample size determination:</b> There are no prior controlled study data to establish the placebo remission rate in PMR. The sample size of 59 per group provides at least 85% and 95% power to detect 25% and 30% treatment difference respectively, assuming 5% to 15% placebo response rate, and using a significance level of 0.05.</p> <p><b>Analysis population:</b> 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.</p> <p>The safety population will include all randomized patients who have received at least one dose or part of a dose of the study medication. All patients will be analyzed according to the treatment they have actually received.</p> <p><b>Primary analysis:</b> The proportion of patients in sustained remission at Week 52 will be analyzed using 2-sided Fisher's exact test. A significance level of 0.05 will be used.</p> <p><b>Analysis of secondary endpoints:</b> Other binary endpoints will be analyzed using the same approach as the primary analysis. Total cumulative prednisone (or equivalent) dose will be analyzed by Wilcoxon rank-sum test. Time to event analysis will use Kaplan-Meier estimates and a log rank test.</p>
<p><b>DURATION OF STUDY PERIOD (per patient)</b></p>	<p>Total duration of study per patient is expected to be approximately 62 weeks:</p> <ul style="list-style-type: none"> <li>• Up to 4 week screening</li> <li>• 52 weeks treatment (double-blind phase)</li> <li>• 6 weeks post-treatment follow-up</li> </ul>

# 1 FLOW CHARTS

## 1.1 GRAPHICAL STUDY DESIGN



Patients will be randomized to one of two groups in a ratio of 1:1

## 1.2 STUDY FLOW CHART

VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 (EOT)	V13 (EOS)
DAY	D-28 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)
WEEK		Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 52	Week 58
<b>Eligibility</b>													
Written informed consent	X												
Inclusion/exclusion criteria <sup>f</sup>	X	X											
Ultrasound central reading <sup>v</sup>	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 <sup>a</sup>		X				X			X		X		
Confirm eligibility		X											
Randomization		X											
Call IRT	X	X		X	X	X	X	X	X	X	X	X	X
<b>Treatment</b>													
Initial treatment kit assignment (IRT)		X											
IMP administration <sup>b</sup>		X <sup>w</sup>	X	X	X	X	X	X	X <sup>s</sup>	X <sup>s</sup>	X <sup>s</sup>		
Concomitant medication review	X <sup>u</sup>	X	X	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 (EOS)
DAY	D-28 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)
WEEK		Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 52	Week 58
Dispense patient diary		X	X	X	X	X	X	X	X	X	X		
Compliance/review patient diary			X	X	X	X	X	X	X	X	X	X	
<b>Vital signs</b>													
Temperature, heart rate, blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X				X			X		X	X	
Height	X												
<b>Efficacy</b>													
PMR clinical assessments (including disease flare)	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician global assessment (MD-VAS)		X				X			X			X	
Patient reported outcomes <sup>c</sup>		X				X			X			X	
Glucocorticoid toxicity index (excl. bone density assessment)		X				X			X		X	X	
Bone density assessment <sup>d</sup>		X										X	
<b>Safety</b>													
AE/SAE recording													
Tuberculosis assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
QuantiFERON®	X												
Chest X-ray <sup>e</sup>	X												
<b>Laboratory testing</b>													
Hematology <sup>f</sup>	X	X		X		X			X		X	X	

VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 (EOT)	V13 (EOS)
DAY	D-28 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)
WEEK		Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 52	Week 58
Chemistry <sup>g</sup>	X	X		X		X			X		X	X	
ANA <sup>h</sup>		X										X	
Fasting lipids <sup>i</sup> and fasting glucose/insulin <sup>j</sup>	X			X		X			X		X	X	
HbA1c	X			X		X			X		X	X	
CRP <sup>k</sup>	X	X	X	X	X	X	X	X	X	X	X	X	
ESR <sup>k</sup>	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis <sup>l</sup>	X												
Virology <sup>m</sup>	X												
Serum pregnancy test <sup>n</sup>	X												
Urine pregnancy test <sup>n</sup>		X		X	X	X	X	X	X	X	X	X	
12-lead ECG	X												
Serum sarilumab <sup>j</sup>		X	X	X		X	X		X <sup>r</sup>			X	X
Antibodies to sarilumab/ADA <sup>j</sup>		X				X			X			X	X
<b>Genotyping and biomarkers<sup>j</sup></b>													
Biomarkers-IL-6 and sIL-6R		X	X			X			X			X	
Immune Cell Phenotyping (Whole Blood) <sup>o</sup>		X		X					X				
Future Use Samples (Serum and Plasma) <sup>p</sup> - <i>Optional</i>		X	X			X			X			X	



VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12 (EOT)	V13 (EOS)
DAY	D-28 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)
WEEK		Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 32	Week 40	Week 52	Week 58
DNA <sup>a</sup> - Optional		X											
RNA <sup>a</sup> - Optional		X	X										

AE = Adverse event; D = Day; DNA = Deoxyribonucleic acid; ECG = Electrocardiogram; EOT = End of treatment; EOS = End of study; EQ-5D = EuroQol; ESR = erythrocyte sedimentation rate; EUL = elevate upper limb; FACIT-Fatigue = Functional assessment of chronic illness therapy fatigue scale; GCA = Giant cell arteritis; GTI = Glucocorticoid toxicity index; HbA1c = Hemoglobin A1c; HBsAg = Hepatitis B surface antigen; HBcore Ab = Hepatitis B core antibodies; HCV = Hepatitis C virus; CRP = C-reactive protein; IL = Interleukin; IMP = Investigational medicinal product; IRT = Interactive voice response system; MD-VAS = Physician global assessment of disease activity- visual analog scale; Pain VAS = Pain visual analog scale; Pt-VAS = Patient global assessment of disease activity- visual analog scale; RNA = Ribonucleic acid; SAE = Serious adverse event; SF-36v2 = Short form 36v2; V = Visit; Wk = Week.

- a Targeted physical examination: head, eyes, ears, neck and throat, skin, respiratory, cardiovascular, neurologic, lymphatic examinations and abdominal examination.
- b Last administration of sarilumab is at Week 50. Patients will be monitored for at least 30 minutes or up to 2 hours as per country specific requirements after each dose of SC IMP for any signs or symptoms of a hypersensitivity reaction.
- c Patient Reported Outcomes include EQ-5D-3L, FACIT-Fatigue, SF-36v2, HAQ-DI
- d Bone Mineral Density assessment will be performed at the baseline (Visit 2) and Week 52 (Visit 12) using a DXA scan. The scan can be performed within ± 14 days of Visit 2 and within -14 days of Visit 12 and 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.
- e Chest X-ray 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 if it does not follow the local guidelines and requirements for active screening of 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.
- f Hematology (blood should 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).
- g Chemistry (blood should 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
- h Anti-nuclear antibody (ANA) will be collected at Visit 2 and EOT visits only.
- i Lipids (blood should be drawn before drug administration): Triglycerides (TG), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol. Fasting is defined as having no food or liquid intake (except water/ice) for six hours or more.
- j Blood should be drawn before drug administration. Fasting is defined as having no food or liquid intake (except water/ice) for six hours or more.
- k CRP and ESR results will be blinded to both Investigator and Sponsor (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 the safety assessor.
- l Urinalysis dipstick: specific gravity, pH, glucose, blood, protein, nitrites, leukocytes, ketones, 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.
- m Human immunodeficiency virus antibodies - if required locally, the locally provided consent for the required HIV screening test will be collected; Hepatitis B: Hep B surface antigen, total Hep B core antibody, Hep B surface antibody, and Hep B viral DNA (if necessary); Hepatitis C: HCV-antibody.
- n In women of child-bearing potential.
- o Immune Cell Phenotyping (Whole Blood): Approximately 40 patients from each of the two treatment arms will be selected for this whole blood draw and immune cell phenotyping analysis.

- p* A separate Future Use Samples Informed Consent has to be obtained before any sampling. Both serum and plasma will be drawn and the samples will be used for future analysis (eg, circulating proteins).
- q* A separate Pharmacogenetic Research Informed Consent for collecting and sequencing DNA and RNA samples has to be obtained before any sampling. One DNA (at baseline or any treatment or follow up visit) and RNA sample for sequencing sampling time point at baseline and pre-dose (V3) are needed.
- r* Additional sample is to be drawn 4-7 days after Week 24 dosing.
- s* Since the visit interval exceeds 4 weeks, interim shipments of IMP to patients home may be performed using direct to patient (DTP) shipping in order to provide the patient with only 4 weeks IMP at a time in order to minimize compliance errors.
- t* If the ultrasound is employed in the diagnosis of PMR, then the ultrasound images need to be submitted to the central reader for confirmation that they fulfill the ultrasound part of the diagnostic criteria for PMR.
- u* For patients who are on >15mg/day (but not exceeding 20mg/day) of prednisone at screening and during the screening period, the Investigator should judiciously taper the prednisone down to 15mg/day prior to randomization in order to prevent a disease flare upon entering the study at 15mg/day of prednisone.
- v* If ultrasound is being used as a diagnostic tool of PMR, the image needs to be submitted to the central reader for confirmation of eligibility.
- w* IMP training. Prior to the first dose of IMP, provide instructions on preparation and self-injection of the pre-filled 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 subcutaneous injections themselves, arrangements must be made for qualified site personnel and/or caregiver to administer study drug every 2 weeks for doses that are not scheduled to be given at the study site.

## 2 TABLE OF CONTENTS

<b>AMENDED CLINICAL TRIAL PROTOCOL 02</b>	<b>1</b>
<b>PROTOCOL AMENDMENT SUMMARY OF CHANGES</b>	<b>2</b>
<b>DOCUMENT HISTORY</b>	<b>2</b>
<b>OVERALL RATIONALE FOR THE AMENDMENT</b>	<b>2</b>
<b>1 FLOW CHARTS</b>	<b>13</b>
1.1 GRAPHICAL STUDY DESIGN	13
1.2 STUDY FLOW CHART	14
<b>2 TABLE OF CONTENTS</b>	<b>19</b>
2.1 LIST OF TABLES	25
<b>3 LIST OF ABBREVIATIONS</b>	<b>26</b>
<b>4 INTRODUCTION AND RATIONALE</b>	<b>27</b>
<b>5 STUDY OBJECTIVES</b>	<b>29</b>
5.1 PRIMARY	29
5.2 SECONDARY	29
5.3 OTHER	29
<b>6 STUDY DESIGN</b>	<b>30</b>
6.1 DESCRIPTION OF THE STUDY	30
6.2 DURATION OF STUDY PARTICIPATION	31
6.2.1 Duration of study participation for each patient	31
6.2.2 Determination of end of clinical trial (all patients)	31
6.3 INTERIM ANALYSIS	31
6.4 STUDY COMMITTEES	32
6.5 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS	32
<b>7 SELECTION OF PATIENTS</b>	<b>33</b>
7.1 INCLUSION CRITERIA	33

7.2	EXCLUSION CRITERIA .....	34
7.2.1	Exclusion criteria related to disease .....	34
7.2.2	Exclusion criteria related to study methodology .....	34
7.2.3	Exclusion criteria related to the current knowledge of Sanofi compound .....	36
<b>8</b>	<b>STUDY TREATMENTS .....</b>	<b>39</b>
8.1	INVESTIGATIONAL MEDICINAL PRODUCT(S) .....	39
8.1.1	Sarilumab or matching placebo: .....	39
8.1.2	Prednisone or matching placebo: .....	41
8.1.3	Add on prednisone taper in the case of flare within initial 12 weeks .....	42
8.2	NONINVESTIGATIONAL MEDICINAL PRODUCT(S) .....	42
8.3	BLINDING PROCEDURES .....	43
8.3.1	Methods of blinding .....	43
8.3.1.1	Blinding of IMP: .....	43
8.3.2	Randomization code breaking during the study .....	44
8.4	METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP .....	44
8.5	INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING .....	45
8.6	STORAGE CONDITIONS AND SHELF LIFE .....	45
8.7	RESPONSIBILITIES .....	46
8.7.1	Treatment accountability and compliance .....	46
8.7.2	Return and/or destruction of treatments .....	47
8.8	CONCOMITANT MEDICATION .....	47
8.8.1	Steroids .....	47
8.8.2	Nonsteroidal anti-inflammatory drugs and analgesics .....	48
8.8.3	Treatment for dyslipidemia .....	48
8.8.4	Glucocorticoid-Induced Osteopenia/Osteoporosis Prevention and Treatment .....	48
8.8.5	CYP Substrates .....	48
<b>9</b>	<b>ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT .....</b>	<b>50</b>
9.1	PRIMARY ENDPOINT .....	50
9.1.1	Primary efficacy endpoint .....	50
9.2	SECONDARY ENDPOINTS .....	51
9.2.1	Secondary efficacy endpoints .....	51
9.2.1.1	Components of sustained remission composite measure at Week 52 .....	51
9.2.1.2	Total cumulative corticosteroid (including prednisone) dose over 52 weeks .....	51

9.2.1.3	Time to first PMR flare .....	52
9.2.1.4	Composite glucocorticoid toxicity index and components .....	52
9.2.2	Safety endpoints .....	52
9.2.2.1	Adverse events .....	52
9.2.2.2	Laboratory safety variables .....	53
9.2.2.3	Chest x-ray .....	53
9.2.2.4	Vital signs .....	54
9.2.2.5	Physical examination .....	54
9.2.2.6	Electrocardiogram variables .....	54
9.3	OTHER EFFICACY ENDPOINTS .....	55
9.3.1	Clinical Outcome Assessments .....	55
9.3.1.1	Patient-Reported Outcomes .....	55
9.3.1.2	Clinician-reported Outcomes .....	56
9.4	PHARMACODYNAMIC .....	56
9.4.1	Pharmacodynamic variables .....	56
9.5	PHARMACOKINETICS AND ANTI-DRUG ANTIBODIES .....	57
9.5.1	Sampling time .....	57
9.5.2	Sample handling procedure .....	57
9.5.3	Bioanalytical method .....	57
9.5.4	Pharmacokinetics parameters .....	58
9.6	PHARMACOGENETIC ASSESSMENT .....	58
9.6.1	Optional stored DNA and RNA samples .....	58
9.7	FUTURE USE OF SAMPLES .....	59
9.8	APPROPRIATENESS OF MEASUREMENTS .....	59
<b>10</b>	<b>STUDY PROCEDURES .....</b>	<b>60</b>
10.1	INDEPENDENT EFFICACY AND SAFETY ASSESSORS .....	60
10.2	VISIT SCHEDULE .....	61
10.2.1	Visit 1: Screening from Day -28 to Day -1 .....	61
10.2.2	Double blind period (52 weeks) .....	62
10.2.2.1	Visit 2/Baseline visit (Day 1, Week 0) .....	62
10.2.2.2	Visit 3 (Day 15±3 Week 2) .....	64
10.2.2.3	Visit 4-11 (Day 29±3 Week 4 to Day 281±3, Week 40) .....	64
10.2.2.4	Visit 12/End of treatment (Day 365±3 Week 52) .....	66
10.2.3	Post-treatment follow-up period (6 weeks) .....	67
10.2.3.1	Visit 13/End of study (Day 407±3, Week 58) .....	67
10.3	DEFINITION OF SOURCE DATA .....	67

10.4	HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION .....	68
10.4.1	Temporary treatment discontinuation with investigational medicinal product (sarilumab or matching placebo).....	68
10.4.2	Permanent treatment discontinuation with investigational medicinal product(s) .....	69
10.4.3	List of criteria for permanent treatment discontinuation .....	69
10.4.4	Handling of patients after permanent treatment discontinuation .....	70
10.4.5	Procedure and consequence for patient withdrawal from study .....	71
10.5	OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING .....	71
10.5.1	Definitions of adverse events .....	71
10.5.1.1	Adverse event .....	71
10.5.1.2	Serious adverse event .....	71
10.5.1.3	Adverse event of special interest .....	72
10.5.2	Serious adverse events waived from expedited regulatory reporting to regulatory authorities.....	74
10.5.3	General guidelines for reporting adverse events .....	74
10.5.4	Instructions for reporting serious adverse events .....	74
10.5.5	Guidelines for reporting adverse events of special interest .....	75
10.5.6	Guidelines for management of specific laboratory abnormalities .....	75
10.5.7	Guidelines for reporting product complaints (IMP) .....	75
10.6	OBLIGATIONS OF THE SPONSOR .....	76
10.7	SAFETY MONITORING.....	76
10.8	SAFETY INSTRUCTIONS .....	77
10.8.1	Infections .....	77
10.8.2	Liver function tests .....	78
10.8.3	Neutrophils .....	79
10.8.4	Platelets .....	79
10.8.5	Systemic hypersensitivity reactions/anaphylaxis .....	80
10.8.6	Diverticulitis and gastrointestinal perforation .....	80
10.8.7	Management of dyslipidemia .....	80
10.8.8	Acute renal failure .....	81
10.9	ADVERSE EVENTS MONITORING .....	81
<b>11</b>	<b>STATISTICAL CONSIDERATIONS .....</b>	<b>82</b>
11.1	DETERMINATION OF SAMPLE SIZE.....	82
11.2	DISPOSITION OF PATIENTS .....	82

11.3	ANALYSIS POPULATIONS .....	83
11.3.1	Efficacy populations .....	83
11.3.1.1	Intent-to-treat /modified intent-to-treat population .....	83
11.3.2	Safety population .....	83
11.3.3	Pharmacokinetic analysis population .....	83
11.4	STATISTICAL METHODS .....	83
11.4.1	Extent of study treatment exposure and compliance .....	84
11.4.1.1	Extent of investigational medicinal product exposure .....	84
11.4.1.2	Compliance .....	84
11.4.2	Analyses of efficacy endpoints .....	84
11.4.2.1	Analysis of primary efficacy endpoint(s) .....	84
11.4.2.2	Analyses of secondary efficacy endpoints .....	85
11.4.2.3	Multiplicity considerations .....	85
11.4.3	Analyses of safety data .....	85
11.4.3.1	Analysis of adverse event data .....	86
11.4.3.2	Analysis of laboratory data .....	86
11.4.3.3	Analysis of vital signs data .....	88
11.4.3.4	Analysis of immunogenicity data .....	88
11.4.4	Analyses of pharmacokinetic and pharmacodynamic variables .....	88
11.4.5	Analyses of patient reported outcomes .....	89
11.5	INTERIM ANALYSIS .....	89
<b>12</b>	<b>ETHICAL AND REGULATORY CONSIDERATIONS .....</b>	<b>90</b>
12.1	ETHICAL AND REGULATORY STANDARDS .....	90
12.2	INFORMED CONSENT .....	90
12.3	HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE .....	91
<b>13</b>	<b>STUDY MONITORING .....</b>	<b>92</b>
13.1	RESPONSIBILITIES OF THE INVESTIGATOR(S) .....	92
13.2	RESPONSIBILITIES OF THE SPONSOR .....	92
13.3	SOURCE DOCUMENT REQUIREMENTS .....	92
13.4	USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST .....	93
13.5	USE OF COMPUTERIZED SYSTEMS .....	93
<b>14</b>	<b>ADDITIONAL REQUIREMENTS .....</b>	<b>94</b>
14.1	CURRICULUM VITAE .....	94

14.2	RECORD RETENTION IN STUDY SITES .....	94
14.3	CONFIDENTIALITY .....	94
14.4	PROPERTY RIGHTS.....	95
14.5	DATA PROTECTION .....	95
14.6	INSURANCE COMPENSATION.....	96
14.7	SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES .....	96
14.8	PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE.....	96
14.8.1	By the Sponsor.....	96
14.8.2	By the Investigator .....	97
14.9	CLINICAL TRIAL RESULTS .....	97
14.10	PUBLICATIONS AND COMMUNICATIONS .....	97
<b>15</b>	<b>CLINICAL TRIAL PROTOCOL AMENDMENTS .....</b>	<b>99</b>
<b>16</b>	<b>BIBLIOGRAPHIC REFERENCES.....</b>	<b>100</b>
<b>17</b>	<b>APPENDICES.....</b>	<b>103</b>
APPENDIX A	STANDARDIZED CORTICOSTEROID-TAPER REGIMEN DURING DOUBLE- BLIND STUDY TREATMENT PERIOD .....	104
APPENDIX B	CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION.....	106
APPENDIX C	COMPOSITE GLUCOCORTICOID TOXICITY INDEX .....	109
APPENDIX D	SPECIFIC LIST FOR GLUCOCORTICOID TOXICITY INDEX.....	115
APPENDIX E	GENERAL GUIDANCE FOR THE FOLLOW-UP OF LABORATORY ABNORMALITIES BY SANOFI.....	117
APPENDIX F	LIST OF OPPORTUNISTIC INFECTIONS.....	120
APPENDIX G	DEFINITION OF ANAPHYLAXIS .....	121
APPENDIX H	FACIT- FATIGUE (PAPER VERSION)* .....	122
APPENDIX I	EUROQOL QUESTIONNAIRE (EQ-5D-3L) (PAPER VERSION)* .....	123
APPENDIX J	SF-36V2 (PAPER VERSION)* .....	126
APPENDIX K	HAQ-DI – HEALTH ASSESSMENT QUESTIONNAIRE (PAPER VERSION)* .....	132



APPENDIX L PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY (PAPER VERSION)* .....	135
APPENDIX M BIOMARKER OBJECTIVES .....	136
APPENDIX N PROTOCOL AMENDMENT HISTORY .....	138

## 2.1 LIST OF TABLES

Table 1 - Summary of investigational medicinal products.....	39
Table 2 - Summary of bioanalytical methods for functional sarilumab and anti- sarilumab antibody .....	58
Table 3 - Power calculations based on total sample size of 118 randomized patients.....	82

### 3 LIST OF ABBREVIATIONS

ADA:	antidrug antibody
AE:	adverse event
AESI:	adverse event of special interest
ANC:	absolute neutrophil count
CRP:	C-reactive protein
CS:	Corticosteroids
CYP:	Cytochrome P450
DMARDs:	disease modifying anti-rheumatic drugs
ECG:	electrocardiogram
eCRF:	electronic case report form
EOT:	end of treatment
hs-CRP:	high-sensitivity C-reactive protein
IEC:	independent ethics committee
IL-6:	Interleukin 6
IMP:	investigational medicinal product
IRB:	institutional review board
IRB/IEC:	institutional review board/independent ethics committee
IRT:	interactive response technology
LDL:	low-density lipoprotein
LFT:	liver function test
PCSA:	potentially clinically significant abnormality
PFS:	prefilled syringe
PMR:	Polymyalgia Rheumatica
q2w:	once in every 2 weeks
RA:	Rheumatoid Arthritis
SAE:	serious adverse events
SC:	subcutaneous
SD:	standard deviation
SF-36v2:	short form 36v2

## 4 INTRODUCTION AND RATIONALE

Polymyalgia Rheumatica (PMR) is a chronic, inflammatory disease of unknown etiology characterized by pain and morning stiffness of the shoulder, neck and pelvic girdle, and is frequently associated with low-grade fever, fatigue, malaise, and weight loss. The debilitating effect of the disease can significantly affect the quality of life of PMR patients. It typically affects individuals older than 50 years, with prevalence varying by age and population (1). In 2008, the number of PMR cases in the US was estimated to be 711,000 (2). The prevalence is higher in women than in men and increases dramatically with age. Based on the only population-based study of PMR in the US, a study in Olmsted County, Minnesota, the prevalence ranged from 21 per 100,000 among persons ages 50–54 years to 4,070 per 100,000 among those age  $\geq 90$  years (2). In Europe, higher rates have been noted in Northern European compared with Southern European populations. In patients who are  $\geq 50$  years of age, annual incidence rates of 50/100,000 were noted in Sweden and 68/100,000 in Denmark compared to 13/100,000 in Italy and 14-19/100,000 in Spain (1).

Although the cause is unknown, both genetic and the environmental factors are thought to be involved. Research suggests that inflammation of the joints and the bursae around these joints leads to the symptoms of pain and stiffness associated with PMR. Although there are no definitive tests, there are guidelines to help in the clinical diagnosis of PMR (3).

Although PMR is typically treated with low doses of corticosteroids (CS), there is a subset of patients who are steroid- dependent or are unable to taper off prednisone or equivalent below 10 mg/day without relapse of symptoms and are therefore at risk of complications of long-term steroid therapy. In the 2015 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) guidelines, the recommended minimum effective starting dose is within the range of 12.5-25 mg of prednisone (or equivalent) daily (4). Mean treatment duration is approximately 2 to 3 years. CS with a slow taper will reduce symptoms rapidly for most patients. However, nearly half of the patients with PMR treated with CS do not respond adequately based on laboratory and clinical markers of disease activity in one report (3) (2010). In another report, among patients with baseline prednisone doses  $>10$  mg/day, only 30% had remission at 1 year (5). Therefore, there exists an unmet medical need in this patient population to spare the toxicities related to chronic CS exposure.

Interleukin 6 (IL-6) plays a key role in the inflammatory responses of PMR (6). Circulating levels of IL-6 are significantly elevated in PMR patients compared to healthy controls. IL-6 signaling leads to the production of acute phase reactants, such as C-reactive protein (CRP) and fibrinogen, which are decreased by anti-IL6R (Interleukin-6 receptor) therapy (7, 8). Persistently elevated CRP levels are observed in PMR patients at relapse (9, 10, 11) and (12).

While not recommended in guidelines for clinical treatment of PMR patients (3) other unproven treatment options, including biologic disease modifying anti-rheumatic drugs (DMARDs), are sometimes used in patients who cannot undergo a slow taper of CS (13). Several biologic anti-inflammatory therapies have been evaluated in Phase 2 clinical trials without success, including secukinumab and canakinumab (14). Evaluation of IL-6R antagonists in Phase 2 clinical trials

suggests blockade of IL-6 signaling may be an effective therapeutic approach for management of PMR (15, 16). These data show that the therapeutic options for patients who cannot tolerate a long course of CS or who are dependent on CS are limited and suggest that IL-6 blockade may provide a treatment option in these patients.

Sarilumab, a fully human immunoglobulin G1 (IgG1) monoclonal antibody, targets IL-6R and inhibits IL-6 signaling. In this study, PMR patients will be treated with sarilumab with CS in order to evaluate the efficacy and safety of sarilumab in patients with PMR.

The efficacy and safety of sarilumab have been evaluated in the phase 2 and phase 3 studies of the rheumatoid arthritis (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 or as monotherapy, respectively. 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 risk of bleeding, clinically evident hepatic injury with elevated hepatic transaminases, and lipid abnormalities and increased risk of MACE. Other potential important risks include increased risk of malignancy and gastrointestinal perforation.

In addition to clinical development for RA, sarilumab has also been studied in patients with ankylosing spondylitis and non-infectious 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 subcutaneously [SC]) once every 2 weeks [q2w]) is selected based largely on the aggregate data from the sarilumab rheumatoid arthritis (RA) clinical development program.

Both 200 mg q2w and 150 mg q2w doses have demonstrated robust clinical efficacy responses in the Phase 3 RA clinical development program, and suppression of biological markers of disease and inflammation similar to those found in PMR patients. While the higher dose has a generally more favorable efficacy response, both doses have acceptable safety profiles (see Investigator Brochure for additional details). Therefore, the dose of sarilumab 200 mg q2w is more likely to provide beneficial effects for patients with PMR and is selected for further evaluation in this study.

## 5 STUDY OBJECTIVES

### 5.1 PRIMARY

To evaluate the efficacy of KEVZARA® (sarilumab) in patients with PMR as assessed by proportion of patients with sustained remission at Week 52 for sarilumab with a 14-week CS tapering regimen as compared to placebo with a 52 week CS tapering regimen.

### 5.2 SECONDARY

- To demonstrate the efficacy of sarilumab (with 14-week taper of CS) compared to placebo (with 52-week taper of CS) in patients with PMR with regards to:
  - Clinical responses (such as components of sustained remission, disease remission rates, time to first disease flare) over time.
  - Cumulative corticosteroid (including prednisone) exposure.
- To assess the safety (including immunogenicity) and tolerability of sarilumab in patients with PMR.
- To measure sarilumab concentrations from serum of patients with PMR.
- To assess the effect of sarilumab on reducing glucocorticoid toxicity as measured by the composite glucocorticoid toxicity index (GTI) questionnaire.

### 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 on a variety of PRO concepts, including fatigue (as measured by FACIT-fatigue scale), health status (as measured by EQ-5D-3L and SF-36v2), physical function (as measured by HAQ-DI), pain (as measured via HAQ-DI by a visual analogue scale [VAS]) and patient assessment of disease activity (as measured via HAQ-DI by a VAS).
- To assess the impact of ESR/CRP levels on remission status.
- To characterize the disease activity of PMR 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 PMR patients while on steroid taper or sarilumab treatment by evaluating circulating proteins, genetics and gene expression in patients who consent for this optional part of the study.

## 6 STUDY DESIGN

### 6.1 DESCRIPTION OF THE STUDY

This is a multicenter, randomized, double-blind, placebo-controlled 52-week, Phase 3 study, evaluating the efficacy and safety of sarilumab in patients with active PMR.

Patients with active PMR who meet the entry criteria will be randomized to the following 2 parallel treatment groups with sarilumab 200 mg or placebo plus protocol-defined CS tapering regimens of either 14 or 52 weeks (as described below and in [Section 9.3.1](#)) in a 1:1 ratio.

- Group 1: Sarilumab 200 mg q2w with a 14 weeks taper of CS
- Group 2: Sarilumab matching placebo q2w with a 52 weeks taper of CS

All patients will receive sarilumab 200 mg or placebo for 52-weeks.

All patients will receive prednisone treatment (CS taper) with different regimen depending on the assigned group (see [Appendix A](#)). Prior to randomization and initiation of study treatment, corticosteroid therapy should be optimized to minimize the risk of serious adverse events associated with tapering of corticosteroids. The initial dose of prednisone for both groups will be 15 mg/day for the first 2 weeks after randomization and then prednisone and/or prednisone matched placebo will be given to patients in order to ensure the double blind CS tapering regimen as defined below.

- Group 1: From Week 2 to Week 13, patients will receive gradually decreasing dose levels of prednisone (prednisone or combination of prednisone and placebo to prednisone (see [Appendix A](#)). From Week 14 onwards, patients without flare will receive prednisone matching placebo.
- Group 2: From Week 2 to Week 51, patients will receive gradually decreasing dose levels of prednisone (prednisone or combination of prednisone and placebo to prednisone (see [Appendix A](#)).

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

During the initial 12 weeks of prednisone taper, treatment for one flare is permitted if it can be successfully treated with a low dose ( $\leq 5$  mg/day) prednisone add-on taper regimen (completed prior to Week 12) and provided that all other sustained remission parameters are met.

For the management of predefined laboratory abnormalities, such as neutropenia, thrombocytopenia, and liver enzymes (Refer to [Section 10.5.6](#) and [Appendix E](#)), study investigators may decide to temporarily hold the study drug (sarilumab or matching placebo) and/or permanently reduce the dose of sarilumab to 150 mg q2w or matching placebo in a continuous blinded manner. A request to reduce dosage will be made in a blinded manner through the IRT system which will implement the request appropriately based on the patient's treatment assignment.

For patients who experience a disease flare and are in need of rescue therapy (such as CS) as per investigator judgment, during the course of the study, they may continue administration of sarilumab or matching placebo in a double-blinded fashion for the full duration of the 52-week treatment period only if corticosteroids are used as rescue therapy (See [Section 8.8](#) for details). 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, corticosteroids 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 non-biological immunosuppressive drugs may be used (patient must have symptomatic PMR disease) and the patient must be discontinued from the study treatment and considered a non-responder.

If the patient or investigator decides to prematurely and permanently discontinue the administration of blinded sarilumab injections and blinded CS tapering regimen, then please refer to [Section 10.4.4](#) for subsequent procedures.

## **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 62 weeks

- An up to 4 weeks screening period
- 52-week treatment period
- A 6-week 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 completed the 52-week double blind treatment period and the follow up period of 6 weeks (Visit 13/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

## 6.4 STUDY COMMITTEES

### *Central review and certification of diagnostic ultrasounds*

If ultrasound is used to diagnose PMR 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 shoulders and hips 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 PMR for their patients.

## 6.5 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS

EFC15160 has been designed as a 52-week, double-blind, placebo-controlled, randomized, study to evaluate the efficacy and safety of sarilumab in patients with active PMR. The 52-week study treatment duration reflects the usual duration of therapy required to ensure sustained remission for patients with PMR (hence, the primary endpoint of sustained remission is at Week 52). The treatment arms are as follows:

- Group 1: Sarilumab 200 mg q2w with a 14-week taper of CS
- Group 2: Sarilumab matching placebo q2w with 52-week taper of CS

Approximately 280 patients who satisfy the eligibility criteria will be enrolled and randomized into 2 parallel arms to receive either sarilumab 200 mg q2w with 14-weeks prednisone taper (Group 1) or sarilumab matching placebo with 52-weeks prednisone taper (Group 2) in the ratio of 1:1. As a result of the inability to recruit due to the COVID19 pandemic, the patient number has been revised to 118.

The ability to taper off of CS rapidly in 14 weeks (as opposed to the usual tapering regimen of a year or more) after initiating therapy while maintaining disease remission with continuing sarilumab alone would represent an important clinically meaningful benefit over usual care.



## 7 SELECTION OF PATIENTS

### 7.1 INCLUSION CRITERIA

I 01. Signed written informed consent.

I 02. Diagnosis of PMR according to the European League against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria as follows (must satisfy all criteria):

- a) Age  $\geq$ 50 years at time of diagnosis.
- b) Bilateral shoulder pain.
- c) Elevated acute phase reactants (CRP  $>$ 10 mg/L and/or ESR  $>$ 30 mm/hr).

AND one of the following:

1. A score  $\geq$ 4 at the time of diagnosis based on the following (without ultrasound):
  - Duration of morning stiffness  $>$ 45 minutes: 2 points.
  - Hip pain or limited range of motion: 1 point.
  - Seronegative for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP): 2 points.
  - Absence of other joint involvement: 1 point.

OR

2. A score  $\geq$ 5 at the time of diagnosis based on the following (with ultrasound):
  - Duration of morning stiffness  $>$ 45 minutes: 2 points.
  - Hip pain or limited range of motion: 1 point.
  - Seronegative for RF and anti-CCP: 2 points.
  - Absence of other joint involvement: 1 point.
  - At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either Posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis: 1 point. (confirmed with ultrasound)
  - Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis: 1 point. (confirmed with 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 03. Patient must be on prednisone of at least 7.5 mg/day (or equivalent) and not exceeding 20 mg/day at screening and during the screening period.
- I 04. Patient is willing and able to receive prednisone of 15 mg/day at randomization.
- I 05. Patient must have a history of being treated for at least 8 weeks with prednisone  $\geq 10$  mg/day or equivalent.
- I 06. Patient must have had at least one episode of unequivocal PMR flare while attempting to taper prednisone at a dose that is  $\geq 7.5$  mg/day (or equivalent) within the past 12 weeks prior to screening:
  - Unequivocal symptoms of PMR flare defined as shoulder and/or hip girdle pain associated with inflammatory stiffness.
- I 07. Patient must have ESR  $\geq 30$  mm/hr or CRP  $\geq 10$  mg/L associated with PMR disease activity within 12 weeks prior to screening.

## 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 disease

- E 01. Diagnosis of Giant Cell Arteritis (GCA) (eg, persistent or recurrent localized headache, temporal artery or scalp tenderness, jaw claudication, extremity claudication, blurry or loss of vision, symptoms of stroke).
- E 02. Concurrent rheumatoid arthritis or other inflammatory arthritis or other connective tissue diseases, such as but not limited to systemic lupus erythematosus, systemic sclerosis, vasculitis, myositis, mixed connective tissue disease, ankylosing spondylitis.
- E 03. Concurrent diagnosis of rhabdomyolysis or neuropathic muscular diseases.
- E 04. Concurrent diagnosis of active fibromyalgia.
- E 05. Inadequately treated hypothyroidism.
- E 06. Organ transplant recipient

### 7.2.2 Exclusion criteria related to study methodology

- E 07. Any prior (within the defined periods below) or concurrent use of immunosuppressive therapies including but not limited to the following:
  - 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.
  - Anakinra within 1 week of baseline.
  - Abatacept within 8 weeks of baseline.
  - Tumor necrosis factor (TNF) inhibitors within 2-8 weeks (etanercept within 2 weeks, infliximab, certolizumab, golimumab, or adalimumab within 8 weeks), or after at least 5 half-lives have elapsed, whichever is longer.
  - Alkylating agents including cyclophosphamide (CYC) within 6 months of baseline.
  - Cyclosporine (CsA), azathioprine (AZA) or mycophenolate mofetil (MMF) or leflunomide within 4 weeks of baseline.
- E 08. Therapeutic failure, including inadequate response or intolerance, or contraindication, to biological IL-6 antagonist (prior IL-6 antagonist treatment that was terminated for reasons unrelated to therapeutic failure at least 3 months before baseline is not exclusionary).
- E 09. Unstable methotrexate (MTX) dose and/or MTX dose >15 mg/week within 3 months of baseline.
- E 10. Concurrent use of systemic CS for conditions other than PMR.
- E 11. 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 12. History of alcohol or drug abuse within 5 years prior to the screening visit.
- E 13. Patient who withdraws consent during the screening period (following signing of the informed consent form).
- E 14. Unable or unwilling to complete the patient-reported outcome (PRO) questionnaires.
- E 15. Patient who meets any of the following conditions/situations:
- Patients with short life expectancy.
  - Conditions/concomitant diseases making patients non-evaluable for the efficacy endpoints (eg, patients with chronic pain).
  - 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.

### 7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

- E 16. Pregnant or breastfeeding woman.
- E 17. Woman of childbearing potential (WOCBP) not protected by highly-effective contraceptive method(s) of birth control (as defined in [Appendix B](#)), and/or who are unwilling or unable to be tested for pregnancy.
- E 18. Exclusion related to Tuberculosis (TB):
- Active TB or a history of incompletely treated TB regardless of screening Quantiferon result
  - 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 (eg, acceptable treatments include 9 months of isoniazid 300 mg oral daily or equivalent proven regimen per local guidelines) or treatment of active tuberculosis infection (TBI) who has obtained consultation with a specialist to rule out active TBI or the need to receive further treatment.
    - Patients with no prior history of chemoprophylaxis for latent TBI or treatment for active TBI but have obtained consultation with a specialist to initiate an appropriate regimen of chemoprophylaxis, based on local epidemiology and applicable guidelines and have demonstrated compliance and tolerated treatment for  $\geq 1$  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 view (See [Section 10.8.1](#)). Additional lateral view is recommended but not required.
  - Suspected extra-pulmonary TB infection regardless of screening Quantiferon result.
  - Patients at high risk of contracting TB, such as close contact with individuals with active or latent TB.
  - Patient who received Bacille Calmette Guerin -vaccination within 12 months prior to screening.
- E 19. 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 virus (progressive multifocal leukoencephalopathy).
- E 20. Patients with fever ( $>38^{\circ}\text{C}$ ) associated with infection, 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 21. Patients with uncontrolled diabetes mellitus, defined as glycosylated hemoglobin (HbA1c)  $\geq 9\%$  at the screening visit.
- E 22. Patients with non-healed or healing skin ulcers.
- E 23. Patients who received any live, attenuated vaccine within 3 months prior to the baseline visit, such as varicella-zoster, oral polio or rubella vaccines.
- E 24. Patients who are positive for hepatitis B surface antigen (HBsAg) or are positive for total hepatitis B core antibody (HBcAb) with negative hepatitis B surface antibody (HBsAb) or are positive for both HBcAb and HBsAb with presence of HBV DNA at screening.
- E 25. Patients who are positive for hepatitis C antibody (HCV Ab).
- E 26. Patients who are positive for human immunodeficiency virus (HIV) antibody test at screening or who previously had a positive HIV antibody test, or who are suspected to be positive for HIV.
- E 27. Patients with a history of recurrent herpes zoster or active herpes zoster.
- E 28. Patients with a history of prior articular or prosthetic joint infection.
- E 29. Prior or current history of malignancy, including lymphoproliferative diseases, other than adequately treated carcinoma in-situ of the cervix, non-metastatic squamous cell or basal cell carcinoma of the skin, within 5 years prior to the baseline visit.
- E 30. 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 31. Patients who have had surgery within 4 weeks prior to the screening visit or with planned surgery during the course of the study.
- E 32. 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 33. Patients with any of the following laboratory abnormalities at the screening visit:
- Hemoglobin  $< 8.5$  g/dL.
  - White blood cells  $< 3000$ /mm<sup>3</sup>.
  - Neutrophils  $< 2000$ /mm<sup>3</sup>.
  - Platelet count  $< 150\ 000$  cells/mm<sup>3</sup>.

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5 x upper limits of normal (ULN).
- 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 Cockcroft-Gault formula).

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

- E 34. 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 investigational medicinal product IMPs are provided in [Table 1](#).

**Table 1 - Summary of investigational medicinal products**

	<b>Name of IMP</b>	<b>Pharmaceutical forms</b>	<b>Dose of drug per administration</b>	<b>Route and method of administration</b>	<b>Treatment duration</b>
Double blind phase of sarilumab	Sarilumab or matching placebo	Single-use 1.14 mL prefilled glass syringes containing 175 mg/mL (200 mg) of sarilumab or placebo solution for injection	Sarilumab 200 mg, or matching placebo	Subcutaneous route	52 weeks
Double blind phase of sarilumab	Sarilumab or matching placebo	Single-use 1.14 mL prefilled glass syringes containing 131.6 mg/ml (150 mg) of sarilumab solution for injection	Sarilumab 150 mg (an option only for patients who had lab abnormality) or matching placebo	Subcutaneous route	In the case of dose reduction
Double blind phase	Prednisone or matching placebo	1 and/ or 5 mg over-encapsulated tablet or over-encapsulated placebo		Oral administration	52 weeks (Combination of prednisone / matching placebo per <a href="#">Appendix A</a> )
Open label ≤5 mg add-on	Prednisone	1 mg Commercial TABLETS		Oral administration	In the case of flare within the first 12 weeks after randomization

#### **Additional detail regarding the method of administration**

##### **8.1.1 Sarilumab or matching placebo:**

###### **Formulation:**

Sarilumab drug product will be provided as single-use 1.14 ml prefilled glass syringes 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 SC in the abdomen or thigh when self-injections or also in upper arm (lateral side) 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 start of the study. 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  $\pm 3$  days is permitted in exceptional circumstances (eg. laboratory test result pending, or an ongoing AE or patient schedule difficulty). For subsequent IMP administrations the initial IMP administration schedule should be followed again (see [Table 1](#)).

An interval of at least 11 days between 2 IMP (sarilumab and matching placebo) 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 the days when the patient has a study visit, the IMP will be administered following clinic procedures and blood collection.

Patients will be monitored for at least 30 minutes after each dose of sarilumab (or up to 2 hours as per country specific requirements) 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 may be reduced to 150 mg q2w in a blinded manner to treat neutropenia, thrombocytopenia and/or elevated liver transaminases. Please see [Section 10.5.6](#) for further details. In addition, sarilumab dose can also be temporarily discontinued as described in [Section 10.4.1](#). The decision to reduce the sarilumab dose and/or to temporarily discontinue it will be made by the investigator.

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:**

#### **Formulation:**

1 and/ or 5 mg over-encapsulated tablet or over-encapsulated matching placebo

#### **Route of Administration:**

Prednisone or matching placebo will be administered orally.

#### **Dose regimen:**

All patients will receive prednisone treatment with different regimen depending on the assigned group (see [Appendix A](#)). Patients will receive prednisone and/or prednisone matching placebo in order to ensure the double-blind CS tapering regimen as defined below is maintained. The initial dose of prednisone for both groups will be 15 mg/day for the first 2 weeks after randomization.

- For Group 1: From Week 2 to Week 13, patients will receive gradually decreasing dose levels of prednisone (see [Appendix A](#)). From Week 14 onwards, patients without flare will receive prednisone matching placebo.
- For Group 2: From Week 2 to Week 51, patients will receive gradually decreasing dose levels of prednisone (prednisone or combination of prednisone and placebo to prednisone) as shown in [Appendix A](#).

There will be 2 phases to each double-blind prednisone taper regimen:

- Phase 1: Initial 2 weeks after randomization (beginning of Week 0 to end of Week 1) when all patients will receive prednisone 15 mg/day.
- Phase 2: 50 weeks (beginning of Week 2 to end of Week 51) following Phase 1. Prednisone and matching placebo will be used to maintain the blinding of the tapering regimen for both treatment arms.

During the prednisone taper, patients will be supplied with monthly kit containing 4 weekly blister packs which will clearly indicate the number of tablets to be taken per day. The monthly kits and blister packs will be numbered, and it is important that the blister packs be used in sequential order and that 7 days of prednisone from each blister be taken by the patient before starting the next blister pack. If a scheduled study visit occurs before the target date, the patient should complete the blister pack assigned for that particularly week before using the sequentially numbered blister packs dispensed at the scheduled study visit. If tablets are missed or skipped, patients should not use the missed tablets before resuming on the blister packs as scheduled.

Patients will be trained in the use of the prednisone treatment kit and 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 in the case of loss of a tablet during dosing. The training must be documented in the patient’s study file.

The daily encapsulated dose may contain prednisone, placebo, or a combination of the two. The number of tablets to be taken each day will vary but will not be consistent with the dosage of prednisone. The number of tablets to be taken daily may increase or decrease during the tapering schedule but will not exceed 6 tablets per day.

In the later stages of the study where visits are more than 1 month apart, an interim visit may be required for IMP dispensing between protocol scheduled on-site visits. As an alternative to these visits, prednisone 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.

Refer to [Appendix A](#) for detailed standardized CS taper regimen during the double-blind study treatment period.

### **8.1.3 Add on prednisone taper in the case of flare within initial 12 weeks**

During the initial 12 weeks of prednisone taper, treatment for one flare before Week 12 is permitted if it can be successfully treated with a low dose of prednisone ( $\leq 5$  mg/day) to add on to the CS tapering regimen provided that all other sustained remission parameters are met. The add-on prednisone must be completed by Week 12.

The prednisone for this add-on taper is provided in an open label manner consisting of 30 count blister (1 mg each) in a child resistant wallet. It is up to the investigator to decide on the CS dosage (with a maximum dose of ( $\leq 5$  mg/day) and taper schedule/duration according to the patient's disease status. The quantity of tablets to be taken daily will be written on the wallet and recorded in the eCRF. The patient will need to be monitored and in close communication with the site to ensure patients have taken the correct quantity of prednisone until the add-on taper is completed prior to Week 12.

## **8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)**

### **Prednisone for rescue therapy**

If a patient experiences a disease flare or cannot adhere to the per protocol prednisone tapering schedule including the 5mg prednisone add-on prior to Week 12, then the patient must stop the per protocol prednisone taper and instead may receive commercial CS as a form of rescue therapy, per investigator's clinical judgment. The commercial CS will be reimbursed by the Sponsor. The patient should continue in the double-blind period of the study for the full 52 weeks and should continue to receive blinded sarilumab or matching placebo injections unless contraindicated by safety concerns and complete the remainder of the study assessments.

Once the patients are on the 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:***

###### **Blinding of Sarilumab**

The list of treatment kit numbers will be generated by the Sanofi Clinical Supplies Department. A patient randomization list will be generated by the interactive response technology (IRT). Both the randomization and treatment kit lists will be loaded into the IRT.

Based on the double blinded study design, the investigators and patients will be blinded to the allocation of the active sarilumab and placebo treatment arms.

Sarilumab and matching placebo will be provided in matching glass prefilled syringes in kits. For example, every 2 weeks, the patient allocated to Group 1 will receive 1 sarilumab prefilled syringe (PFS), the patient allocated to Group 2 will receive a sarilumab matching placebo PFS.

The treatment kit numbers will be obtained by the Investigator at the time of patient randomization and subsequent patient scheduled visits via IRT that will be available 24 hours a day.

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. Please refer to [Section 10.6](#) for suspected unexpected adverse drug reaction unblinding by the Sponsor.

A dose reduction from 200mg to 150mg for sarilumab treatment can be requested by the Safety Assessor in the case of laboratory abnormalities. IRT system will apply the dose reduction in a blinded manner only if the patient is receiving the 200 mg dose such that the Efficacy Assessor is unaware of the request for dose reduction.

###### **Blinding of Prednisone**

Based on the double-blind study design, the investigators and patients will be blinded to the allocation of the different protocol defined CS-taper regimens.

Prednisone will be provided in blister pack suitable for double blinding as per assigned protocol defined CS-taper regimen. For example, every week, the patient will take the PS supplied in 1 blister package.

The list of treatment kit numbers will be generated by the Sanofi Clinical Supplies Department. A patient randomization list will be generated by the IRT. 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 subsequent patient scheduled visits via IRT that will be available 24 hours a day.

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.

### **8.3.2 Randomization code breaking during the study**

In case of an adverse event (AE), the code may only be broken in circumstances when knowledge of the IMP (Sarilumab and Prednisone) 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 complete an EOT visit (Visit 12) that should be scheduled at the time of the treatment discontinuation, if possible. If not possible, the EOT visit should be scheduled as soon as possible after treatment discontinuation. The IRT should be notified of EOT.

Knowledge of certain laboratory data may result in inadvertent unblinding of a patient's treatment. In order to maintain the blind, an Independent Safety Assessor, who is the only individual who can have access to laboratory data (except post-baseline CRP), will be assigned at the study site to perform regular review of the patient's laboratory data.

At the facilities where the PK measurements, 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 randomization treatment kit number is generated centrally by Sanofi. The IMPs are packaged in accordance with this list. Patients will be randomized to one of the two 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 treatment number has been provided by the IRT.

Patients who meet the entry criteria will be randomized to one of the two treatment groups at a ratio of 1:1.

At the screening Visit 1 (Day -28 to D-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, D1), after confirming the patient is eligible for entry into the treatment period, the site coordinator will contact the IRT 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 may be rescreened once upon investigator discretion. Upon rescreen, a different patient identification will be issued. There is no requirement for a waiting period between the screen-failure and the re-screening dates. The IRT report will flag rescreened patients. Patients who are re-screened must sign a new consent form and the Visit 1 procedures must be repeated (except chest X-ray if one was taken within 12 weeks of the new V1 (rescreen date) that clearly documents the exclusion of TB or if local guidelines and requirements for active screening of TB are followed). 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 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 IMPs 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 DTP (direct to patient) 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 for sarilumab or matching placebo (whether empty or unused) are returned by the patient at each visit when a treatment dispensing is planned.
  - Except for the prefilled syringes that 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 prefilled syringes will be used for drug accountability purposes.
- All 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**

All used, partially-used or unused treatments will be retrieved by the Sponsor. A detailed treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

A detailed treatment log of the destroyed IMP 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 CONCOMITANT MEDICATION**

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

The use of any biologics for treatment of PMR during the study is not permitted throughout the study treatment and until 6 weeks following the last 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 remain in the study and continue to be monitored for safety.

Administration of any live (attenuated) vaccine is contraindicated until 3 months following the last sarilumab or matching placebo administration.

Treatment with non-biological disease modifying anti-rheumatic drugs [DMARDs] (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, corticosteroids 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 non-biological immunosuppressive drugs may be used (patient must have symptomatic PMR disease) and the patient must be discontinued from the study treatment and considered a non-responder.

Methotrexate with a dose not exceeding 15 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 for safety reasons, if necessary), 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 CS defined by protocol is not permitted.

### **8.8.1 Steroids**

There will be two standardized prednisone-tapering regimens in this study with one that lasts for 14 weeks (Group 1) and the other one lasting for 52 weeks (Group 2) ([Appendix A](#)). The total

duration of prednisone therapy for each particular patient will depend on the treatment group to which the patient is randomized.

If the patient develops an AE for a condition not related to PMR that requires the introduction of a new systemic CS medication, the new medication and AE must be recorded on the patient eCRF. Furthermore, the Sponsor must be notified as soon as possible at the time of the steroid dose modification (eg, within 24 hours) in order to discuss the patient's status with regards to ongoing study participation. Intranasal, inhaled, ophthalmic or topical CSs as per label are permitted throughout the course of the study.

### **8.8.2 Nonsteroidal anti-inflammatory drugs and analgesics**

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

Acetaminophen use should be limited to  $\leq 4$  g every 24 hours. Specific attention should be paid to co-administration of hepatotoxic drugs.

### **8.8.3 Treatment for dyslipidemia**

Treatments for dyslipidemia, such as statins, are permitted. Doses of medications for dyslipidemia should be stable for at least 6 weeks prior to screening visit. Any change and reason for change should be recorded on the patients' electronic case report form (eCRF). 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 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 bisphosphonate therapy (eg, alendronate 70 mg weekly or zoledronate 4 mg annually) for the prevention or treatment of glucocorticoid-induced osteoporosis are permitted. The doses and treatment duration should comply with local practice or clinical guidelines at the discretion of the Investigator.

### **8.8.5 CYP Substrates**

IL-6 has been shown to reduce Cytochrome P450 (CYP)1A2, 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 CYP450 enzymes could be normalized, and as a result drugs that are metabolized by these CYP450 isoforms may have decreased levels when PMR 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, cyclosporine, 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®).

## 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:

1. Achievement of disease remission no later than Week 12

AND

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

AND

3. Sustained reduction of CRP (to  $<10$  mg/L, with an absence of successive elevations to  $\geq 10$  mg/L) from Week 12 through Week 52

AND

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

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 less than or equal to 100mg (or equivalent), such as those employed to manage an AE not related to PMR.

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

Note: A single CRP elevation ( $\geq 10$  mg/L) is not considered absence of remission unless CRP remains elevated ( $\geq 10$  mg/L) for two consecutive study visits.

#### Signs and symptoms of PMR

Evaluation for clinical signs and symptoms by the Efficacy Assessor at every study visit according to the schedule of assessment should include, but are not limited to, the following:

- Morning stiffness and/or pain, in the neck, shoulder and/or hip girdles
- Limited range of motion of the shoulders and/or hip girdles
- Constitutional symptoms, such as fatigue, weight loss and low-grade fever
- Other features judged by the clinician-investigator to be consistent with a PMR flare

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

Increase in CS dose is defined as:

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

*Note: During the initial 12 weeks of prednisone taper, treatment for one flare before Week 12 is permitted if it can be successfully treated with a low dose ( $\leq 5$  mg/day) prednisone add-on taper regimen (completed prior to Week 12) and provided that all other sustained remission parameters are met.*

### **Blinding of CRP and ESR assessment results**

Investigators including Efficacy Assessors, patients and sponsor will remain blinded on C-reactive protein (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 the 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 the efficacy assessment of study patients.

## **9.2 SECONDARY ENDPOINTS**

### **9.2.1 Secondary efficacy endpoints**

#### **9.2.1.1 Components of sustained remission composite measure at Week 52**

- Patients who achieved of disease remission by Week 12.
- Patients who have absence of disease flare from Week 12 through Week 52.
- Patients who have normalization of CRP (decrease to  $<10$  mg/L) with sustained normalization from Week 12 through Week 52.
- Patients who successfully adhere to the prednisone taper from Week 12 through Week 52.

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 less than or equal to 100mg (or equivalent), such as those employed to manage an AE not related to PMR.

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

The total cumulative prednisone (or equivalent) dose over the 52-week period for each group will be analyzed as a secondary endpoint.

### **9.2.1.3 Time to first PMR flare**

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

### **9.2.1.4 Composite 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, lipid metabolism, bone mineral density, glucocorticoid-induced myopathy, skin toxicity, neuropsychiatric toxicity and infection. These are the potential CS toxicities that are likely to occur during the course of a clinical trial 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 and the specific list of the GTI will be assessed at baseline, Week 12 (Visit 6), Week 24 (Visit 9), Week 40 and Week 52 (except bone density which will be assessed at Baseline and Week 52 only). Glucocorticoid toxicity or the changes in GC toxicity (comparison with baseline data) for each domain will be scored (score range from -36 to 439) based on the information from laboratory, vital sign and clinical assessments and review of concomitant medications. 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.

Bone Mineral Density assessment will be performed at the baseline (Visit 2) and Week 52 (Visit 12) using a Dual-Energy X-ray Absorptiometry (DXA) scan. The scan can be performed within  $\pm 14$  days of Visit 2 and within -14 days of Visit 12 and 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.

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 (refer to [Appendix C](#)). Information related to the domains/items of the Specific List will be collected if available at the scheduled time points (baseline, Week 12, Week 24, Week 40 and Week 52), but no pre-specified assessments related to the domains in the Specific List (refer to [Appendix D](#)), unless for cause, 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 10.5.1.1](#) 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 in 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 (ANC) 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 only at screening (Visit 1), baseline (Visit 2) and End of Treatment (EOT) visits.
- Fasting lipids: total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides.
- Fasting glucose, insulin and HbA1c.
- For women of child-bearing potential: serum pregnancy test Beta-HCG at screening (Visit 1) and urine pregnancy tests during the remainder of the study.
- QuantiFERON® -TB Gold evaluation (screening visit only).
- HIV-1/HIV-2 antibody testing (screening visit only).
- Hepatitis B and C serology (screening visit, or in case of liver injury): Hepatitis B: HBsAg, total HBcAb, HBsAb, and HBV DNA (if necessary); Hepatitis C: HCV Ab.
- Urinalysis including specific gravity, pH, glucose, ketones, blood, protein, nitrites, 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-sarilumab antibody (see [Section 9.5.2](#))

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 if it does not follow the local guidelines and requirements for active screening of 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 scarring 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.

#### **9.2.2.4 Vital signs**

Vital signs include temperature, BP, and heart rate. They will be collected at every site visit prior to IMP administration. Weight will be collected at the screening Visit 1 (Day -28 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  $\geq 38^{\circ}\text{C}$ ) associated with infections 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 -28 to Day -1) and Visit 12 (Week 52) or early termination visit, and a targeted physical examination will be performed at the 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 screening Visit 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 are asked to complete the patient-reported outcome (PRO) questionnaires described below at Visit 2 (baseline visit), Visit 6 (Week 12), at Visit 9 (Week 24), and Visit 12 (Week 52) (see [Section 1.1](#) and [Section 1.2](#)). Translations of the PRO questionnaires, where not already available, will follow industry best practices ([17](#)).

##### 9.3.1.1.1 *The functional assessment of chronic illness therapy fatigue scale*

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 ([18](#)). See [Appendix H](#).

##### 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). 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’ ([19](#)). Refer to [Appendix I](#).

##### 9.3.1.1.3 *Short form 36v2 (SF-36v2)*

The Short Form 36v2 (SF-36v2) is a short-form generic, 36-item PRO instrument that evaluates 8 multi-item dimensions of health ([20](#)): 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 ([21](#)). Refer to [Appendix J](#).

##### 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:

1. Sum the 8 category scores by using the highest sub-category score from each category.
2. Adjust for use of aids/devices and/or help from another person when indicated.
3. 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 two 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. Refer to [Appendix K](#).

### **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 not active and 100 is considered the most active (refer to [Appendix L](#)).

## **9.4 PHARMACODYNAMIC**

### **9.4.1 Pharmacodynamic variables**

- Changes in ESR and CRP from baseline through Week 52.
- Changes in IL-6 level and soluble IL-6 receptor (sIL-6R) 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 M](#)).
  - 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 cell phenotyping. Approximately 80 patients (40 patients from each treatment arm) will be selected for this analysis. Please refer to Lab Manual for details.
  - Disease activity assessment of PMR patients will be assessed via evaluation of circulating proteins and gene expression.



1. Future Use Samples (Optional): Serum or plasma samples will be collected at V2 (baseline), V3 (Week 2), V6 (Week 12), V9 (Week 24), V12 (Week 52 EOT) for circulating protein measurements (a separate future use sample informed consent needs to be obtained).
2. Pharmacogenetic (Optional): DNA samples will be collected at V2 (Baseline), or any treatment or follow up visit, RNA samples will be collected at V2 (Baseline) and/or pre-dose at V3 (Week 2) (refer to [Section 1.2](#)) for gene expression measurement (a separate pharmacogenetics informed consent needs to be obtained; refer to [Section 9.6.1](#)).

For all patients, samples will be collected for assessment of PD parameters including but not limited to, CRP, ESR, IL-6 and sIL-6R levels, and immune cell phenotyping. The Investigator is discouraged from testing IL-6 locally. Samples will be taken pre-dose if taken on a dosing day (see [Appendix M](#)).

## 9.5 PHARMACOKINETICS AND ANTI-DRUG ANTIBODIES

### 9.5.1 Sampling time

Pre-dose blood samples at each study visit will be collected for determination of serum sarilumab concentration (functional), and antibodies to sarilumab as designated on the randomized treatment period study flow chart (see [Section 1.2](#)). The date of collection should be recorded in the patient eCRF.

*Note: Serum sarilumab concentrations (functional), and anti sarilumab 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 antidrug antibody (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.

### 9.5.2 Sample handling procedure

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

### 9.5.3 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 anti- sarilumab antibody**

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

ELISA = enzyme-linked immunosorbent assay

### 9.5.4 Pharmacokinetics parameters

Pre-dose serum sarilumab concentrations at Week 0 and sarilumab trough levels at Weeks 2, 4, 12, 16, 24, 32, 52 and Week 58 will be collected. In addition, post-dose sample will be taken 4-7 days after the Week 24 (Visit 9).

## 9.6 PHARMACOGENETIC ASSESSMENT

### 9.6.1 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 M](#) for further details).

The blood DNA and RNA sample, and the DNA and RNA 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 and RNA 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.

## 9.7 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 9.6.1](#)). 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](#)) for the purposes of evaluating circulating proteins. Additional details will be provided in the laboratory manual (refer [Appendix M](#) for further details).

These samples will remain labelled with the same identifiers used during the study (ie, subject 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](#)).

## 9.8 APPROPRIATENESS OF MEASUREMENTS

The key to assessing the effectiveness of a novel therapy for PMR is to determine its ability to reduce the cumulative dose of CS used which in turn results in fewer CS associated toxicities while able to maintain disease remission. To this end, the primary endpoint is a composite one that assesses the ability to achieve a sustained disease remission by Week 12 with sarilumab while adhering to predefined prednisone taper that represents a substantial reduction in prednisone exposure compared to the current standard of care. It also assesses the durability of sarilumab's treatment response (maintenance of remission) over an extended period of time compared to the current usual prednisone regimen, which is an important factor for a chronic disease like PMR. The secondary endpoints evaluate specific components of the primary endpoint.

One of the other efficacy endpoints utilizes the GTI for the first time in a study of PMR patients to assess if there is less CS associated toxicity with sarilumab that employs a substantially shorter CS tapering regimen than the conventional CS tapering regimen per standard of care. Lastly, the patient and clinician reported outcomes will further evaluate the potential clinical benefits of sarilumab for the treatment of PMR.

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 PMR patients. The PK and PD assessments will provide additional information related to the exposure of sarilumab and biological effect of sarilumab in PMR 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 the sites. An overview of those definitions is provided below.

#### Efficacy Assessor

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

- Assessment of clinical signs and symptoms of PMR (without access to any central laboratory data including CRP and ESR)
- Assessment of adherence to the protocol defined prednisone taper regimen or management of investigator-led open-label prednisone use (including the use of prednisone add-on and/or rescue corticosteroids per protocol) or other rescue therapy use

The Efficacy Assessor should not have access to any central laboratory data. 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 separate 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 and initiate rescue CS in order to properly manage disease activity, if necessary. In such a scenario, the SC IMP will continue per protocol unless 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 re-initiate 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  $\pm 3$  day visit window. In general, PRO assessments should be completed at the study site as part of the visit (per study flow chart) 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.

### **10.2.1 Visit 1: Screening from Day -28 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.
- Assess patient based upon inclusion and exclusion criteria.
- Record patient demographic data.
- Review medical, surgical, smoking and alcohol history.
- Review prior and concomitant medication history.
  - For patients who are on  $>15\text{mg/day}$  (but not exceeding  $20\text{mg/day}$ ) of prednisone at screening and during the screening period, the Investigator should judiciously taper the

prednisone down to 15mg/day prior to randomization in order to prevent a disease flare upon entering the study at 15mg/day of prednisone.

- Review family cardiovascular history.
- Perform full physical examination.
- Perform PMR clinical assessments.
  - If the ultrasound is employed in the diagnosis of PMR, then the ultrasound images need to be submitted to the central reader for confirmation that they fulfill the ultrasound part of the diagnostic criteria for PMR.
- Perform tuberculosis assessment.
- Perform blood sampling (fasting) for the following tests:
  - Hematology, chemistry
  - Fasting lipids, fasting glucose or insulin
  - HbA1c
  - CRP
  - ESR
  - Virology
  - Serum  $\beta$ -hCG pregnancy test (for WOCBP)
  - Quantiferon Gold Testing. (Refer to [Section 10.8.1](#))
  - Urinalysis (dipstick)
  - Measure vital signs (including systolic and diastolic BP [mmHg], heart rate [beats per minute] and body temperature [ $^{\circ}$  C]).
  - Measure body weight [kg].
  - Measure height [cm].
  - Obtain 12-lead ECG.
  - Perform chest x-ray. (Refer to [Section 9.2.2.3](#) and [Section 10.8.1](#))
  - Schedule a Visit 2 within 28 days (maximum) from Visit 1.

## **10.2.2 Double blind period (52 weeks)**

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

- Review and record concomitant medication use.
- Confirm eligibility by review of Inclusion/Exclusion Criteria
- If the patient meets all 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, SF-36v2, FACIT-Fatigue, 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
- Measure vital signs (including systolic and diastolic BP [mmHg], heart rate [beats per minute] and body temperature [°C]).
- Measure body weight [kg].
- Perform PMR clinical assessment for disease activity and flare.
- Complete physician global assessment (MD-VAS).
- Inquire about AEs/SAEs.
- Perform Tuberculosis assessment.
- Perform targeted physical examination (including head, eyes, ears, neck and throat, skin, respiratory, cardiovascular, neurologic, lymphatic examinations and abdominal examination).
- Complete Glucocorticoid Toxicity Index questionnaire.
- Perform DXA scan (may be performed within  $\pm 14$  days of this visit) Not required if previously performed within 12 weeks of baseline visit. Refer to [Section 9.2.1.4](#) for details.
- Perform blood sampling (fasting, prior to administration of IMP) for the following tests:
  - Hematology and chemistry
  - ANA
  - CRP
  - ESR
  - Serum sarilumab and antibodies to sarilumab
  - Biomarkers IL-6, sIL-6R
  - Immune cell phenotyping (whole blood)
  - Future Use Samples for serum and plasma (Optional - requires separate signed consent form)
  - Pharmacogenetic samples for DNA and RNA (Optional - requires separate signed consent form)
- Perform urine pregnancy test (for women of childbearing potential).
- 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 pre-filled syringes and the use of the weekly blister packs of prednisone. Document this training in the patient study file. Note: If the patient is unable or unwilling to perform the subcutaneous injections themselves, arrangements must be made for qualified site personnel and/or caregiver to administer 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 each dose of SC IMP for any signs or symptoms of a hypersensitivity reaction.
- Schedule an appointment for Visit 3.

#### **10.2.2.2 Visit 3 (Day 15±3 Week 2)**

- Review concomitant medication.
- Dispense new patient diary and review last visit patient diary.
- Measure vital signs (including systolic and diastolic BP [mmHg], heart rate [beats per minute] and body temperature [°C]).
- Perform PMR clinical assessment for disease activity and flare.
- Inquire about AEs/SAEs.
- Perform tuberculosis assessment.
- Perform blood sampling (prior to administration of IMP) for the following tests:
  - CRP
  - ESR
  - Serum sarilumab
  - Biomarkers IL-6, sIL-6R
  - Future Use Samples – Serum and Plasma (Requires separate signed consent form)
  - Pharmacogenetic samples for RNA (Requires separate signed consent form)
- Dispense and administer IMP.
- Patients will be monitored for at least 30 minutes or up to 2 hours as per country specific requirements after each dose of SC IMP for any signs or symptoms of a hypersensitivity reaction
- Schedule an appointment for next visit.

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

- Call IRT to register visit.



- Administer PRO questionnaires (EQ-5D-3L, 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], heart rate [beats per minute] and body temperature [°C]).
  - Measure body weight (kg) (Applicable only at Visits 6, 9 and 11)
  - Perform PMR clinical assessment for disease activity and flare.
  - Complete physician global assessment (MD-VAS) at Visits 6 and 9 only.
- Inquire about AEs/SAEs.
- Perform tuberculosis assessment.
  - Perform 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**).
  - Complete Glucocorticoid Toxicity Index questionnaire. (**Applicable only at Visits 6, 9 and 11**).
- Perform blood sampling at all visits (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 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.
- Perform blood sampling (prior to administration of IMP) for the following tests:
  - Anti-sarilumab antibody (Applicable only at Visits 6 and 9).
  - Biomarkers IL-6, sIL-6R. (Applicable only at Visits 6 and 9).
  - Immune Cell Phenotyping – Whole Blood (Applicable only at Visits 4 and 9).

- Future Use Samples – Plasma and Serum (Optional - requires separate signed consent form) (Applicable only at Visits 6 and 9).
- Perform urine pregnancy test (for WOCBP).
- Dispense and administer IMP.
- Patients will be monitored for at least 30 minutes or up to 2 hours as per country specific requirements after each dose of IMP for any signs or symptoms of a hypersensitivity reaction.
- Schedule an appointment for the next planned study 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, SF-36v2, FACIT-Fatigue, and 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 from the patient.
- Review concomitant medication.
- Review last visit patient diary.
- Measure vital signs (including systolic and diastolic BP [mmHg], heart rate [beats per minute] and body temperature [°C]).
- Measure body weight [kg].
- Perform PMR clinical assessment for disease activity and flare.
- Complete physician global assessment (MD-VAS).
- Inquire about AEs/SAEs.
- Perform tuberculosis assessment.
- Perform full physical examination.
- Complete Glucocorticoid Toxicity Index questionnaire.
- Perform DXA scan (may be performed within -14 days of this visit). Refer to [Section 9.2.1.4](#) for details.
- Perform blood sampling (fasting) for the following tests:
  - Hematology and chemistry.
  - ANA.
  - Fasting lipids, fasting glucose and insulin.
  - HbA1c.
  - CRP.
  - ESR.

- Serum sarilumab and antibodies to sarilumab.
- Biomarkers IL-6, sIL-6R.
- Future Use Samples – Plasma and Serum (Requires separate signed consent form).
- Perform urine pregnancy test (for WOCBP).
- Schedule an appointment for Visit 13 (EOS).

### **10.2.3 Post-treatment follow-up period (6 weeks)**

#### **10.2.3.1 Visit 13/End of study (Day 407±3, Week 58)**

- Call IRT to register visit.
  - Review concomitant medication.
  - Perform PMR clinical assessment for disease activity and flare.
- Inquire about AEs/SAEs.
  - Perform tuberculosis assessment.
  - Perform blood sampling for the following tests:
    - Serum sarilumab and antibodies to sarilumab.

### **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 CRFs and in device capturing questionnaires and scales will be part of source data:

- Local laboratory reports.
- EuroQol (EQ-5D).
- MD-VAS.
- FACIT-F.
- HAQ-DI.
- Erythrocyte sedimentation rate results.
- SF-36v2.

Additional data that are considered to be part of source data are:

- Chest x-ray or signed documented x-ray and reports.

- Chest MRI.
- Ultrasound images.
- Patient Home Dosing Diaries.
- ECG tracings and reports.
- Central lab reports.  
Local lab reports and ESR results  
DXA results  
Diagnostic results from other healthcare professionals, if appropriate, for PMR 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.

##### **10.4.1 Temporary treatment discontinuation with investigational medicinal product (sarilumab or matching placebo)**

Temporary treatment discontinuation may be considered because of suspected AEs. Re initiation of treatment with the IMP (SC and/or oral) will be done under close and appropriate clinical/and or laboratory monitoring once it is considered 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](#)).

Temporary SC IMP treatment discontinuation corresponds to  $\geq 1$  dose not administered to the patient.

A temporary discontinuation of SC IMP  $\geq 31$  consecutive days will be considered permanent.

The following is a list of criteria for temporary discontinuation (refer to [Section 10.8](#) for details):

- Increase in ALT level to  $\geq 3$  x ULN to  $\leq 5$  x ULN and total bilirubin  $\leq 2$  x ULN will result in temporary IMP discontinuation. 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's judgement. The IMP may be resumed at the same dose or at a lower dose of 150 mg q2w in such cases if the patient was randomized to the 200 mg group (see [Section 10.8.2](#) and [Appendix E](#)).
- Decrease in neutrophil count to a level  $\geq 500/\text{mm}^3$  to  $< 1000/\text{mm}^3$  without signs of infection. The IMP (sarilumab or matching placebo) can be resumed only after the neutrophils have returned to a value  $\geq 1000/\text{mm}^3$  and all requirements for resumption of study drug administration are met based on investigator's judgement. The IMP may be

resumed at the same dose or at a lower dose of 150 mg q2w in such cases if the patient was randomized to the 200 mg group (see [Section 10.8.3](#) and [Appendix E](#)).

- Decrease in platelet count to a level of  $\geq 50\ 000$  cells/mm<sup>3</sup> to  $< 100\ 000$  cells/mm<sup>3</sup> without spontaneous bleeding. The IMP can be resumed only after the platelet count is  $\geq 100\ 000$ /mm<sup>3</sup> and all requirements for resumption of study drug administration are met based on investigator's judgement. The IMP may be resumed at the same dose or at a lower dose of 150 mg q2w in such cases if the patient was randomized to the 200 mg group (See [Section 10.8.4](#) and [Appendix E](#)).
- Inter-current 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 re-expose the patient to the IMP (sarilumab or matching placebo) at any time during the study, or from the patient not to be re-exposed to the IMP whatever the reason. Oral IMP (prednisone) may be permanently discontinued and replaced with rescue CS but the IMP may continue in this case upon the discretion of the Dual Assessors as long as safety is not compromised. However, if IMP is permanently discontinued then oral IMP must be permanently discontinued as well.

#### **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.

All IMP will be permanently discontinued in case of the following events (refer to [Section 10.8.2](#), [Section 10.8.3](#), and [Section 10.8.4](#) for details):

- Opportunistic infections (as assessed by the investigator) including, but not limited to, active tuberculosis and non-tuberculosis mycobacteria infections.
  - The diagnosis of tuberculosis can be made either on symptoms or on a chest radiograph suggestive of active tuberculosis. 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 non-tuberculosis mycobacteria.
- The patient is at risk through close contact with a person with active tuberculosis and the patient refuses to undergo tuberculosis evaluation.
- Symptoms of systemic hypersensitivity or anaphylactic reactions.
- Severe neurologic disease such as demyelinating disease or PML.
- Significant laboratory abnormalities resulting in permanent IMP discontinuation:

- ALT > 5 x ULN or ALT > 3 x ULN with concomitant total bilirubin > 2 x ULN (unless patient has documented Gilbert's Syndrome).
- Neutrophil count < 500/mm<sup>3</sup>, or neutrophil count < 1000/mm<sup>3</sup> with evidence of infection.
- Platelet count < 50 000/mm<sup>3</sup>, or platelet count < 100 000/mm<sup>3</sup> with evidence of bleeding.
- Acute renal failure (refer to [Section 10.8.8](#)).
- 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.
- Diagnosis of GCA (eg, persistent or recurrent localized headache, temporal artery or scalp tenderness, jaw claudication, extremity claudication, blurry or loss of vision, symptoms of stroke).

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 end of treatment (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 associated with 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 for at least 6 weeks after last dose of SC IMP and for primary endpoint and key secondary endpoints 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 non-patient 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 patients no longer wish to take the IMP, they will be encouraged to remain in the study. 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 sections of the eCRF 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 re-contact 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 re-randomized (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. Reconciliation of AEs between the GTI and clinical safety database will be part of the usual data review surveillance activities.

##### **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.
- Alanine aminotransferase >3 x ULN and total bilirubin >2 x ULN or asymptomatic ALT increase >5 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.
- Suspected transmission of an infectious agent.
- GCA.

#### **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. AESI 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 B](#)).
- Symptomatic overdose (serious or nonserious) with 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.
- Increase in alanine transaminase (ALT)  $\geq 3$  x ULN (see the “Increase in ALT” flow diagram in [Appendix E](#)).
- 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 F](#) 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, 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 pre-specified 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 the 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 (serious or non-serious), 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 E](#).

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

- Neutropenia.
- Thrombocytopenia.
- Increase in ALT.

#### **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 [suspected unexpected serious adverse reaction]), 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 Investigator's brochure 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 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 MONITORING**

### **Signs and symptoms of GCA**

Additionally, at every study visit signs and symptoms of GCA including but not limited to the following should be assessed:

- Localized headache, temporal artery or scalp tenderness, jaw claudication, extremity claudication, blurry or loss of vision, symptoms of stroke.
- Other features judged by the clinician-investigator to be consistent with a GCA diagnosis.

If the diagnosis of GCA is highly suspected or confirmed, please discontinue IMP permanently and manage the patient appropriately. The GCA should be reported as an SAE. The patient should remain in the study and complete the remainder of the study visits per protocol.

## 10.8 SAFETY INSTRUCTIONS

### 10.8.1 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 TEAEs were infections (mostly non-serious 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 adverse event 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 form. 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 10.5.5](#)). Infections requiring prolonged treatment (>14 days) or anti-TB medication are considered AESI. 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 sarilumab label. 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 if it does not follow the local guidelines and requirements for active screening of 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 scarring 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  $\gamma$ ) 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.

### 10.8.2 Liver function tests

Please refer to [Section 10.5.5](#) for liver function test (LFT) abnormalities to be reported as AESI.

The Sponsor relies on investigators', particularly Safety Assessors', judgment for adapting concomitant medication in case of LFT abnormalities.

In order to closely follow LFTs, assessment of ALT, AST, alkaline phosphatase, and bilirubin (total, conjugated) are performed per specifications on the study flow charts (see flow chart [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 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 E](#)).
- If ALT is  $\geq 3$  x ULN and  $\leq 5$  x ULN and bilirubin is  $\leq 2$  x ULN, administration of SC IMP must be temporarily interrupted, and LFTs 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 SC IMP administration are met (see [Appendix E](#)).
- The SC IMP will then be restarted at the Safety Assessor's discretion after conditions for resumption of IMP administration are met (ALT  $<3$  x ULN). Safety assessor will have the options of either to restart the SC IMP at its current dose or to perform a dose reduction

request in a blinded manner through IRT for patients without a previous reduction in dose. Dose of sarilumab will then be reduced to 150 mg if the patient was randomized to the 200 mg group.

### 10.8.3 Neutrophils

Refer to [Section 10.5.5](#) criteria for reporting neutropenia as an AESI.

In case of a decrease in neutrophil count to a level  $\geq 500/\text{mm}^3$  and  $< 1000/\text{mm}^3$ :

- The IMP (sarilumab or matching placebo) may temporarily discontinued; the patient must be assessed for evidence of infection and CBC blood test repeated within 48 hours from the Safety Assessor's awareness of neutrophil count  $\geq 500/\text{mm}^3$  and  $< 1000/\text{mm}^3$ .
- Discontinuation of SC IMP is maintained until the neutrophil count returns to  $\geq 1000/\text{mm}^3$  (see [Appendix E](#)).
- After the patient meets all requirements for resumption of SC IMP administration, including neutrophil count  $\geq 1000/\text{mm}^3$ , then SC IMP administration may resume. The safety assessor will have the options of either to restart the SC IMP at its original dose or to perform a dose reduction request in a blinded manner through IRT. The dose of sarilumab will be reduced to 150 mg if the patient was randomized to the 200 mg group.

In case of a decrease in neutrophil count  $< 1000/\text{mm}^3$  with signs of infection or neutrophil count  $< 500/\text{mm}^3$ :

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

### 10.8.4 Platelets

Refer to [Section 10.5.5](#) for criteria for reporting thrombocytopenia as an AESI.

In case of a decrease in platelet count to a level  $\geq 50\ 000/\text{mm}^3$  and  $< 100\ 000/\text{mm}^3$ :

- The IMP (sarilumab or matching placebo) must be temporarily discontinued; the patient must be assessed for evidence of spontaneous bleeding and CBC blood test repeated within 48 hours from the Safety Assessor's awareness of platelet count  $\geq 50\ 000/\text{mm}^3$  and  $< 100\ 000/\text{mm}^3$ .
- Discontinuation of SC IMP is maintained until the platelet count returns to  $\geq 100\ 000/\text{mm}^3$  (see [Appendix E](#)).

- After the patient meets all requirements for resumption of SC IMP administration, including platelet count  $\geq 100\ 000/\text{mm}^3$ , then SC IMP administration may resume. The Safety Assessor will have the option of either to restart the SC IMP at its original dose or to perform a dose reduction request in a blinded manner through IRT. The dose of sarilumab will be reduced to 150 mg if patient was randomized to the 200 mg group.

The SC IMP must be permanently discontinued if platelet count is  $< 50\ 000/\text{mm}^3$  (confirmed by repeat testing) or if  $< 100\ 000/\text{mm}^3$  with spontaneous bleeding (see [Section 10.4.2](#)).

### **10.8.5 Systemic hypersensitivity reactions/anaphylaxis**

Severe systemic hypersensitivity reactions (in rare cases, fatal anaphylaxis) have been reported with biologics, including tocilizumab. Rare, severe non-fatal systemic hypersensitivity reactions have been observed with sarilumab. The patient should be monitored for 30 minutes or up to 2 hours as per country specific requirements after the IMP (sarilumab or matching placebo) 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 or up to 2 hours as per country specific requirements 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 G](#) 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.

### **10.8.6 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 will be reported as an SAE (see [Section 10.5.4](#)). Confirmed diverticulitis or gastrointestinal ulceration should be reported as AEs.

### **10.8.7 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 in this population of PMR patients treated with anti-IL-6R antagonists is unknown.



As such, patients who are found to have dyslipidemia during the course of the study should be treated according to the NCEP/ATP3 or applicable local guideline. Also see [Section 8.8.3](#) under concomitant medication rules for lipid lowering therapy.

#### **10.8.8 Acute renal failure**

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

### **10.9 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 compared between the sarilumab and placebo groups. There are no prior controlled study data to establish the placebo remission rate in PMR. A 25% difference from placebo response rate is considered clinically relevant, and the initial sample size of 140 per group provides at least 90% power to detect such a difference regardless of the placebo response rate, using a two-sided  $\chi^2$  test at a significance level of 0.01. Data from the GIACTA trial in a related population with GCA suggest that such a treatment difference is achievable (22).

As a result of the inability to recruit due to the COVID19 pandemic, the power calculations have been revised for the decreased sample size from 140 per group to 59 per group, and the change in statistical significance level from 0.01 to 0.05.

Table 3 shows the power calculations for sample size of 118 based on a two-sided  $\chi^2$  test at a significance level of 0.05. The sample size of 59 per group provides at least 85% and 95% power to detect a 25% and 30% between group difference respectively, assuming placebo response rates between 5% to 15%.

**Table 3 - Power calculations based on total sample size of 118 randomized patients**

<b>Assumed sustained remission rate for placebo + 52-week prednisone taper</b>	<b>Sample Size per group</b>	<b>Power assuming an absolute 25% between group difference</b>	<b>Power assuming an absolute 30% between group difference</b>	<b>Minimal detectable difference</b>
5%	59	95.6%	98.8%	11.1%
10%	59	91.2%	97.2%	13.5%
15%	59	86.9%	95.4%	15.1%

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 /modified intent-to-treat population***

Intent-to-treat (ITT) population: all randomized population 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:

- Non-randomized 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 be 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 one post-dose, non-missing serum sarilumab concentration.

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

## **11.4 STATISTICAL METHODS**

Analysis of the randomization double-blind phase is described below. The post-treatment 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 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 (sarilumab or matching placebo) will be summarized for each treatment group descriptively as a quantitative variable (N, Mean, standard deviation [SD], Median, Min, and 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 (sarilumab or matching placebo) 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:

$100 \times \text{total number of injections administered} / [\text{nominal number of injections for the duration of double-blind exposure}]$ .

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 (refer to [Section 9.1.1](#)) is the proportion of patients achieving sustained remission at Week 52 compared between sarilumab and placebo analyzed in the ITT population. The primary endpoint will be summarized as counts and proportions in each treatment group and analyzed by Fisher's exact test. Patients who do not achieve remission, receive rescue treatment with open label prednisone (or equivalent), withdraw from the study before Week 52, or having missing data that prevents assessment of the primary endpoint will be considered as non-responders. The significance level for all tests will be 0.05 (2-sided).

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 (defined in [Section 9.2.1](#)) will be analyzed as described for the primary endpoint (see [Section 11.4.2.1](#)).

The cumulative prednisone (or equivalent) dose will be analyzed using a non-parametric Wilcoxon rank-sum test and the mean and median dose summarized.

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

The GTI assessment (total score and domain-specific scores) will be analyzed as other secondary efficacy endpoint using the mixed model repeated measures (MMRM) approach. The model includes treatment, visit, treatment-by-visit interaction as fixed effects, and baseline score as a covariate, will be used to test the difference of the 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 95% CI and the p-value will be provided.

#### **11.4.2.3 Multiplicity considerations**

If the primary endpoint reaches statistical significance, then secondary endpoints will be tested in a fixed sequential order to maintain an overall type I error rate of 0.05. Details of the hierarchical testing approach will be specified in the statistical analysis plan.

#### **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.

#### 11.4.3.2.1.1 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:  $\geq 1.5$  Giga/L – LLN.
- Grade 2:  $\geq 1.0$  – 1.5 Giga/L
- Grade 3:  $\geq 0.5$  – 1.0 Giga/L.
- Grade 4:  $< 0.5$  Giga/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. Dose will be reduced to 150 mg if patient was randomized to the 200 mg group.

#### 11.4.3.2.1.2 Assessment of potential drug-induced liver injury

The liver function tests, 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 ( $> 3$  x ULN), time to onset of the initial AST elevation ( $> 3$  x ULN), time to onset of the initial total bilirubin elevation ( $> 2$  x ULN), and time to first observation of ALT  $> 3$ ULN 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 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

Summarize the normalization by parameter (to  $\leq 1$  ULN or return to baseline) of elevated LFTs by categories of elevation (1- $< 3$  x, 3 x, 5 x, 10 x, 20 x ULN for ALT and AST, 1.5 x ULN for Alkaline phosphatase, and 1.5 x and 2 x 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 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 immunogenicity data**

At each sample time, the result of the ADA assay will be categorized as either positive or negative. ADA positive samples will be further characterized as either neutralizing or non-neutralizing. Descriptive statistics will be provided for:

ADA positive patients are defined as:

- Treatment Emergent Responses: Patients with no positive assay response at baseline but with a positive assay response during the TEAE period or
- Treatment Boosted Responses: Patients with a positive ADA assay response at baseline and also have at least a 4-fold increase in titer over baseline titer during the TEAE period.

ADA negative patients are defined as any evaluable patient that is not an ADA positive patient.

Descriptive statistics for ADA titers will be provided for patients with positive ADA assay response and selected sub-categories.

Efficacy/safety endpoints will be analyzed for the subgroup of ADA positive patients during the TEAE period and compared to ADA negative patients.

#### **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, standard error of the mean (SEM), coefficient of variation (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 (all data is continuous):

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

The model, including treatment, visit, treatment-by-visit interaction, 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 95% CI and the p-value will be provided.

#### **11.5 INTERIM ANALYSIS**

No interim analysis is planned for this study.

## **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 Sub-Investigator, 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 (institutional review board/independent 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, if required by local laws, for those who are able to be consented but not able to sign the form), 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, from a guardian, minor, etc.), the method should be specified following the ICH requirements. The first part of the section should be adapted, keeping the point as appropriate.

Prior to the optional collection of blood for pharmacogenetics, the pharmacogenetic informed consent form must be obtained from the patient. This process includes a signing of the form with the name spelled out, and personally dated by the patient (or by the patient's legally acceptable representative, if required by local laws, for those who are able to be consented but not able to sign the form), and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the patient.

Similarly, prior to the optional collection of blood (plasma/serum) for Future Use Samples the informed consent form must be obtained from the patient in the same manner described above. Both informed consent forms for pharmacogenetics and Future Use Samples 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**

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, informed consent form, Investigator's Brochure 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 Investigator's Brochure 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 Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators 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 pre-identified 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 curriculum vitae 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 per local requirements) 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 Investigator's Brochure, 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 Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the clinical trial.

The Investigator and the Sub-Investigators 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 /Sub-Investigator 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 Sub-Investigators 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 twelve (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 re-collected if necessary.

## 16 BIBLIOGRAPHIC REFERENCES

1. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, Miranda-Fillooy JA, Gonzalez-Juanatey C, Martin J, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. *Arthritis Rheum.* 2009;61(10):1454-61.
2. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum.* 2008;58(1):26-35.
3. Dasgupta B, Borg FA, Hassan N, Barraclough K, Bourke B, Fulcher J, et al. BSR and BHPR guidelines for the management of polymyalgia rheumatic. *Rheumatology.* 2010;49(1):186-90.
4. Dejaco C, Duftner C, Buttgerit F, Matteson EL, Dasgupta B. The spectrum of giant cell arteritis and polymyalgia rheumatica: Revisiting the concept of the disease. *Rheumatology.* 2017;56(4):506-15.
5. Caporali R, Cimmino MA, Ferraccioli G, Gerli R, Klersy C, Salvarani C, et al. Systemic plus methotrexate for polymyalgia rheumatica: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 2004;141(7):493-500.
6. Buttgerit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia rheumatic and giant cell arteritis: A systematic review. *JAMA.* 2016;315(22):2442-58.
7. Huizinga TW, Fleischmann RM, Jasson M, Radin AR, Van Adelsberg J, Fiore S, et al. Sarilumab, a fully human monoclonal antibody against IL-6R $\alpha$  in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomized SARIL-RA-MOBILITY Part A trial. *Ann Rheum Dis.* 2014;73(9):1626-34.
8. Genovese MC, Fleischmann R, Kivitz AJ, Rell-Bakalarska M, Marticova R, Fiore S, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: Results of a Phase III study. *Arthritis Rheumatol.* 2015;67(6):1424-37.
9. Pulsatelli L, Boiardi L, Pignotti E, Dolzani P, Silvestri T, Macchioni P, et al. Serum interleukin-6 receptor in polymyalgia rheumatic: A potential marker of relapse/recurrence risk. *Arthritis Rheum (Arthritis Care & Research).* 2008;59(8):1147-54.
10. Dasgupta B, Panayi GS. Interleukin-6 in serum of patients with polymyalgia rheumatica and giant cell arteritis. *Rheumatol.* 1990;29(6):456-8.
11. Cutolo M, Straub RH, Foppiani L, Prete C, Pulsatelli L, Sulli A, et al. Adrenal gland hypofunction in active polymyalgia rheumatic, effect of glucocorticoid treatment on adrenal hormones and interleukin 6. *J Rheumatol.* 2002;29(4):748-56.

12. Cantini F, Salvarani C, Oliveiri I, Macchioni L, Ranzi A, Niccoli L, et al. Erythrocyte sedimentation rate and C-reactive protein in the evaluation of disease activity and severity in polymyalgia rheumatic: A prospective follow-up study. *Semin Arthritis Rheum.* 2000;30(1):17-24.
13. Caylor TL, Perkins A. Recognition and management of polymyalgia rheumatica and giant cell arteritis. *Am Fam Physician.* 2013;88(10):676-84.
14. Matteson EL, Dasgupta B, Schmidt WA, Salvarani C, Gendi N, Galeazzi M, et al. A 2-week single-blind, randomized, 3-arm proof of concept study of the effects of secukinumab (anti-IL17 mAb), canakinumab (anti-IL-1 b mAb), or corticosteroids on initial disease activity scores in patients with PMR, followed by an open-label extension to assess safety and effect duration. American College of Rheumatology Annual Meeting (abstract #885). 2014.
15. Toussirot E, Martin A, Soubrier M, Redeker S, Regent A. Rapid and sustained response to tocilizumab in patients with polymyalgia rheumatica resistant or intolerant to glucocorticoids: A multicenter open-label study. *J Rheumatol.* 2016;43(1);249-51.
16. Devauchelle-Pensec V, Berthelot JM, Cornec D, Renaudineau Y, Marhadour T, Jousse-Joulin S, et al. Efficacy of first-line tocilizumab therapy in early polymyalgia rheumatica: a prospective longitudinal study. *Ann Rheum Dis.* 2016;75(8):1506-10.
17. Diane Wild, Alyson Grove, Mona Martin, Sonya Eremenco, Sandra McElroy, Aneesa Verjee-Lorenz, Pennifer Erikson. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: Report of the ISPOR Task Force for Translation and Cultural Adaptation Report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value in Health* 2005;8(2).
18. Cella D, Nowinski C.J. Measuring quality of life in chronic illness: The Functional Assessment of Chronic Illness Therapy measurement system. *Archives of Physical Medicine and Rehabilitation,* 2002;83:S10-7.
19. EUroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16(3):199-208
20. John E. Ware, Jr. and Cathy Donald Sherbourne. The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual Framework and Item Selection. *Medical Care.* 1992;30(6):473-483
21. Maruish ME (2011) User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI: QualityMetric Incorporated.
22. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of tocilizumab in giant-cell arteritis. *NEJM.* 2017;377(4):317-28.
23. Arnold The sensitivity and specificity of reduced CD8 lymphocyte levels in the diagnosis of polymyalgia rheumatic/giant cell arteritis. *Clinical and experimental rheumatology.* 1993;11(6):629-34

24. Van der Geest Disturbed B Cell Homeostasis in Newly Diagnosed Giant Cell Arteritis and Polymyalgia Rheumatica *A&R* 2014;66(7):1927-38.
25. Dasgupta. Interleukin-6 in serum of patients with polymyalgia rheumatic and giant cell arteritis. *Annals of the Rheumatic Diseases*, 1989;48, 307-311
26. Taboada. Clonally Expanded CD8 T Cells in Patients with Polymyalgia Rheumatica and Giant Cell Arteritis. *Clinical immunology and immunopathology* 1996;79(3)
27. Corrigan. The sequential analysis of T-Lymphocyte subsets and Interleukin-6 in Polymyalgia Rheumatica patients as predictors of disease remission and steroid withdrawal. *British Journal of Rheumatology*. 1997;36:976-980
28. Van Sleen. Involvement of Monocyte Subsets in the Immunopathology of Giant Cell Arteritis. *Scientific Reports*. 2017;7:6553.
29. Ribbens. Increased matrix metalloproteinase-3 serum levels in rheumatic diseases: relationship with synovitis and steroid treatment. *ARD*. 2002;61:161-6
30. Kim. Intercellular adhesion molecule-1 (ICAM-1, CD54) is increased in adhesive capsulitis. *J Bone Joint Surg Am*. 2013;95(23):e181-8
31. Roche. Correlation of Interleukin-6 production and disease activity in Polymyalgia Rheumatica and Giant Cell Arteritis. *Arthritis & Rheumatism*. 1993;36(9):1286-94
32. Uddhammer. Cytokines and adhesion molecules in patients with Polymyalgia Rheumatica. *British Journal of Rheumatology*. 1998;37:766-69
33. Cantanoso. Treatment of Refractory Polymyalgia Rheumatica With Etanercept: An Open Pilot Study *A&R*. 2007;57(8):1514-19

## **17 APPENDICES**

**Appendix A Standardized corticosteroid-taper regimen during double-blind study treatment period**

<b>Week</b>	<b>Group 1-Daily PS dose 14 weeks taper</b>	<b>Group 2-Daily PS dose 52 weeks taper</b>
0 Day 1	15	15
1	15	15
2	14	14
3	12	12
4	10	12
5	9	12
6	8	10
7	7	10
8	6	9
9	5	9
10	4	9
11	3	9
12	2	8
13	1	8
14	PS placebo	8
15	PS placebo	8
16	PS placebo	7
17	PS placebo	7
18	PS placebo	7
19	PS placebo	7
20	PS placebo	6
21	PS placebo	6
22	PS placebo	6
23	PS placebo	6
24	PS placebo	5
25	PS placebo	5
26	PS placebo	5
27	PS placebo	5
28	PS placebo	4



<b>Week</b>	<b>Group 1-Daily PS dose14 weeks taper</b>	<b>Group 2-Daily PS dose 52 weeks taper</b>
29	PS placebo	4
30	PS placebo	4
31	PS placebo	4
32	PS placebo	3
33	PS placebo	3
34	PS placebo	3
35	PS placebo	3
36	PS placebo	2
37	PS placebo	2
38	PS placebo	2
39	PS placebo	2
40	PS placebo	2
41	PS placebo	2
42	PS placebo	2
43	PS placebo	2
44	PS placebo	1
45	PS placebo	1
46	PS placebo	1
47	PS placebo	1
48	PS placebo	1
49	PS placebo	1
50	PS placebo	1
51	PS placebo	1

## **Appendix B Contraceptive guidance and collection of pregnancy information**

### **DEFINITIONS**

#### **Non reproductive potential**

1. Premenopausal female with 1 of the following:
  - 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**

A WOCBP should avoid pregnancy and should use the highly effective contraceptive methods detailed below through the course of the entire study and until 12 weeks after the last dose of sarilumab or matching placebo.

**Female subjects:**

<p><b>Highly Effective Contraceptive Methods That Are User Dependent</b></p> <p><i>Failure rate of &lt;1% per year when used consistently and correctly</i></p>
<ul style="list-style-type: none"> <li>• Combined (estrogen- and progestogen-containing ) hormonal contraception associated with inhibition of ovulation             <ul style="list-style-type: none"> <li>• oral</li> <li>• intravaginal</li> <li>• transdermal</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• Progestogen-only hormone contraception associated with inhibition of ovulation             <ul style="list-style-type: none"> <li>• oral</li> <li>• injectable</li> <li>• implantable</li> </ul> </li> </ul>
<p><b>Highly Effective Methods That Are User Independent</b></p>
<ul style="list-style-type: none"> <li>• Implantable progestogen-only hormone contraception associated with inhibition of ovulation</li> </ul>
<ul style="list-style-type: none"> <li>• Intrauterine device</li> </ul>
<ul style="list-style-type: none"> <li>• Intrauterine hormone-releasing system</li> </ul>
<ul style="list-style-type: none"> <li>• Bilateral tubal occlusion</li> </ul>
<ul style="list-style-type: none"> <li>• Vasectomized partner</li> </ul>
<ul style="list-style-type: none"> <li>• Sexual abstinence if this is the preferred and usual lifestyle of the subject</li> </ul>

*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 sterilisation (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 effective contraception include:*

- Intra-uterine devices (IUD);
- Hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release).

Male participants with partners of reproductive potential who become pregnant

- The Investigator will attempt to collect pregnancy information on any female partner of a male participant who becomes pregnant while participating in this study. This applies only to male participants 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 participants who become pregnant

- The Investigator will collect pregnancy information on any female participant, 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 the 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.

## Appendix C COMPOSITE Glucocorticoid Toxicity Index

<p><b>1. Body Mass Index (BMI) (compared to baseline)</b></p> <ul style="list-style-type: none"><li>a. Improvement in the direction of the normal range by more than 2 BMI units [normal range = 18.5-24.9 kg/m<sup>2</sup>]</li><li>b. No significant change (BMI remains within +/- 2 BMI units compared with baseline) OR BMI remains within the normal range</li><li>c. Moderate increase in BMI (increase by more than 2 but less than 5 BMI units, to above the upper limit of normal BMI [24.9 kg/m<sup>2</sup>])</li><li>d. Major increase in BMI (increase by at least 5 but less than 8 BMI units above normal BMI [24.9 kg/m<sup>2</sup>])</li></ul>
<p><b>2. Glucose Tolerance (compared to baseline)</b></p> <ul style="list-style-type: none"><li>a. Improvement in glucose tolerance:<ul style="list-style-type: none"><li>• HbA1c declined &gt;10% from baseline without medication increase OR</li><li>• Decrease in diabetic medication without an increase in HbA1c of &gt;10% or HbA1c &lt; 5.7%</li></ul></li><li>b. No significant change in glucose tolerance:<ul style="list-style-type: none"><li>• HbA1c within 10% of baseline or HbA1c &lt; 5.7% AND no change in medication OR</li><li>• HbA1c increased to &gt; 10% of baseline with a decrease in medication OR</li><li>• HbA1c decreased by &gt; 10% of baseline with an increase in medication</li></ul></li><li>c. Worsening of glucose tolerance or medication status:<ul style="list-style-type: none"><li>• HbA1c &gt; 5.7% and increased to &gt;10% of baseline without a change in medication OR</li><li>• Increase in diabetic medication with &lt; 10% increase in HbA1c</li></ul></li><li>d. Worsening of glucose tolerance despite increased treatment:<ul style="list-style-type: none"><li>• HbA1c &gt; 5.7% AND increased to &gt;10% of baseline AND an increase in diabetic medication</li></ul></li></ul>
<p><b>3. Blood Pressure (BP) (compared to baseline)</b></p> <ul style="list-style-type: none"><li>a. Improvement in BP:<ul style="list-style-type: none"><li>• Decrease in BP of &gt;10% of baseline without medication increase, unless baseline systolic BP ≤ 120 and diastolic BP ≤ 85 OR</li><li>• Decrease in medication without an increase in BP of &gt;10%, unless baseline systolic BP ≤ 120 and diastolic BP ≤ 85</li></ul></li><li>b. No significant change in BP:<ul style="list-style-type: none"><li>• BP within 10% of baseline or systolic BP ≤ 120 and diastolic BP ≤ 85 AND no change in medication OR</li><li>• Increase in either systolic or diastolic BP &gt;10% with a decrease in medication OR</li><li>• Improvement in systolic or diastolic BP of &gt; 10% with an increase in medication</li></ul></li><li>c. Worsening of hypertension:</li></ul>

<ul style="list-style-type: none"> <li>• Increase in BP of &gt;10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg without a change in medication OR</li> <li>• An increase in anti-hypertensive medication accompanied by stability or no significant change in both the systolic and diastolic BP</li> </ul> <p>d. Worsening of hypertension despite treatment:</p> <ul style="list-style-type: none"> <li>• Increase in BP of &gt;10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg AND an increase in medication</li> </ul>
<p><b>4. Lipid metabolism (low-density lipoprotein [LDL] compared to baseline)</b></p> <p>a. Improvement in lipids:</p> <ul style="list-style-type: none"> <li>• Decrease in LDL concentration &gt;10% of baseline toward the target range without medication increase OR</li> <li>• Decrease in medication without an increase in LDL of &gt;10% or LDL remains within target range</li> </ul> <p>b. No significant change in LDL:</p> <ul style="list-style-type: none"> <li>• LDL within 10% of baseline or within the target range for patient AND no change in medication OR</li> <li>• Increase in LDL &gt; 10% with a decrease in medication OR</li> <li>• Improvement in LDL of &gt; 10% with an increase in medication</li> </ul> <p>c. Worsening of LDL or medication status:</p> <ul style="list-style-type: none"> <li>• Increase in LDL of &gt;10% to above target range without a change in medication OR</li> <li>• Increase in medication with &lt;10% change in LDL</li> </ul> <p>d. Worsening of LDL despite treatment:</p> <ul style="list-style-type: none"> <li>• Increase in LDL of &gt;10% AND an increase in medication</li> </ul>
<p><b>5. Bone Mineral Density (compared to baseline)</b></p> <p>a. Improvement – increase in BMD by &gt;3%</p> <p>b. No significant change (BMD between -3% and +3%)</p> <p>c. Deterioration - decrease in BMD (BMD decrease by &gt;3%)</p> <p><i>% refers to total BMD in gms/cm<sup>2</sup></i></p>
<p><b>6. Glucocorticoid-induced myopathy</b></p> <p>a. No steroid myopathy</p> <p>b. Mild steroid myopathy (weakness WITHOUT functional limitation)</p> <p>c. Moderate steroid myopathy (weakness WITH functional limitation)</p> <p><b>See Steroid Myopathy definitions, below</b></p>
<p><b>7. Skin</b></p> <p>a. No skin toxicity</p> <p>b. Mild skin toxicity</p> <p>c. Moderate skin toxicity</p>

2

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

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

<b>Skin 6b. Mild</b>	<b>Skin 6c. Moderate</b>	<b>Severe (Specific Domain)</b>
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

<b>7b. Mild</b>	<b>7c. Moderate</b>	<b>Severe (Specific Domain)</b>
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
<b>Body Mass Index</b> - An absolute increase in BMI of more than 8 units (and >24.9 kg/m <sup>2</sup> )		
<b>Blood Pressure</b> - Hypertensive emergency (see definition, below) - PRES (Posterior reversible encephalopathy syndrome) (see definition, below)		
<b>Endocrine</b> - Symptomatic adrenal insufficiency		
<b>Bone Health</b> - Osteonecrosis of one joint - Osteonecrosis of more than one joint - Bone mineral density decrease > 6% - Insufficiency fracture - Insufficiency fracture in more than one bone		
<b>Muscle &amp; Tendon</b> - Severe glucocorticoid myopathy (see definition) - Tendon rupture - More than one tendon rupture		
<b>Eye</b> - 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)		

<b>Infection</b> - Grade 4 infection (see definition, below) - Grade 5 infection (death from infection)		
<b>Glucose Tolerance</b> - Diabetic nephropathy - Diabetic neuropathy - Diabetic retinopathy		
<b>Gastrointestinal Tract</b> - Gastrointestinal perforation (occurring in the absence of regular nonsteroidal anti-inflammatory drug use) - Peptic ulcer disease confirmed by endoscopy (excluding <i>H. pylori</i> )		
<b>Skin</b> - Severe skin toxicity (see definition, below)		
<b>Neuropsychiatric</b> - 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		
<b>Other glucocorticoid toxicities</b>  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 surface 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

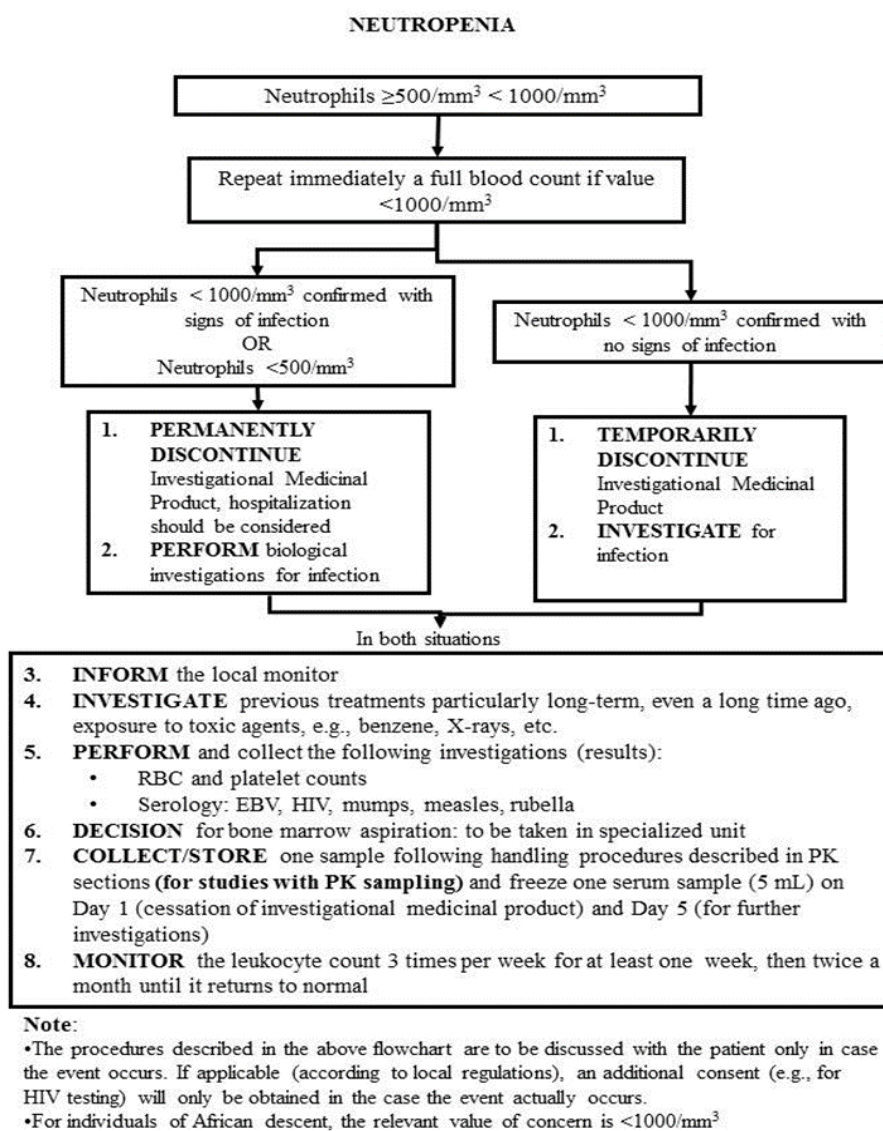
#### References

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

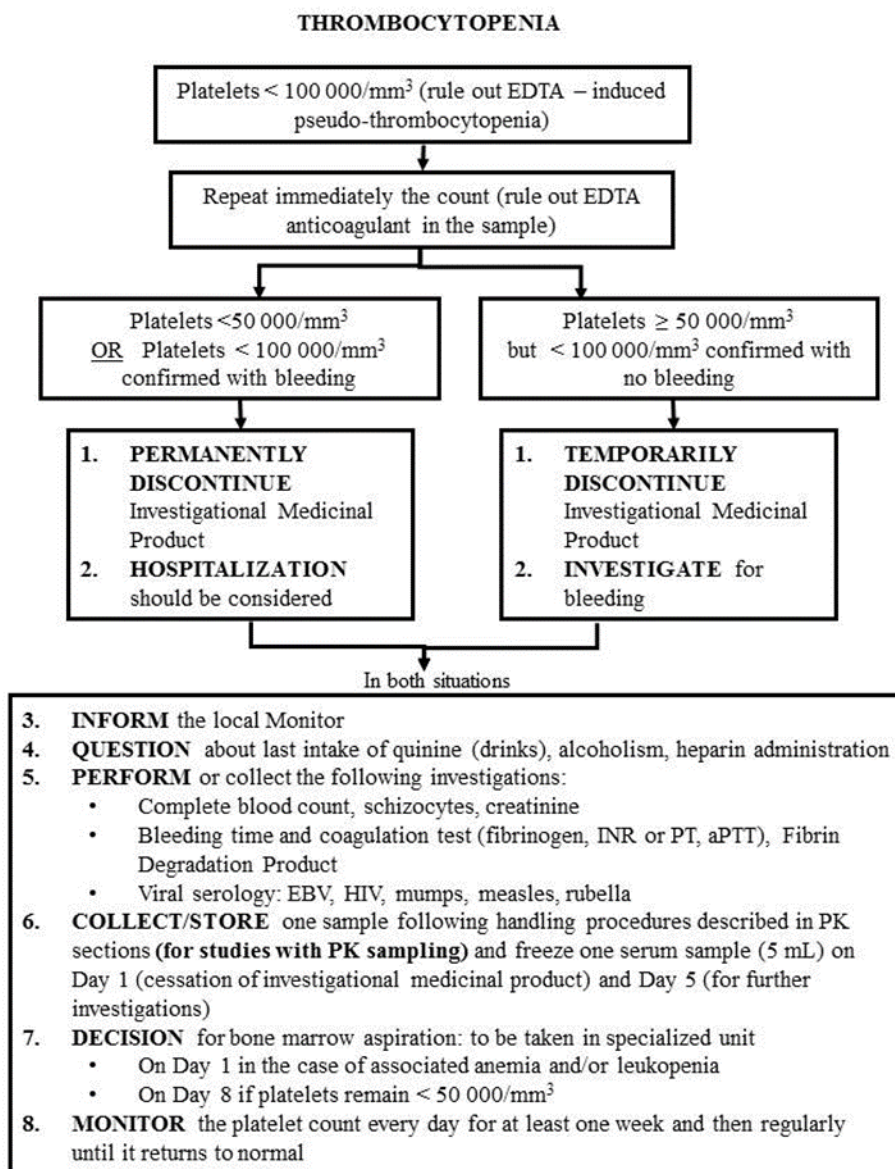
Medical Research Council of the United Kingdom. Guide to Examination of the Peripheral Nervous System: Memorandum No 45. Palo Alto, Calif: Pedragon House; 1978.

American Heart Association. Hypertensive Crisis. Accessed [http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/Hypertensive-Crisis\\_UCM\\_301782\\_Article.jsp#.V0NnSzv2ZaQ](http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/Hypertensive-Crisis_UCM_301782_Article.jsp#.V0NnSzv2ZaQ). 5/1/2015.

## Appendix E 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 adverse events in [Section 10.4.3](#) is met

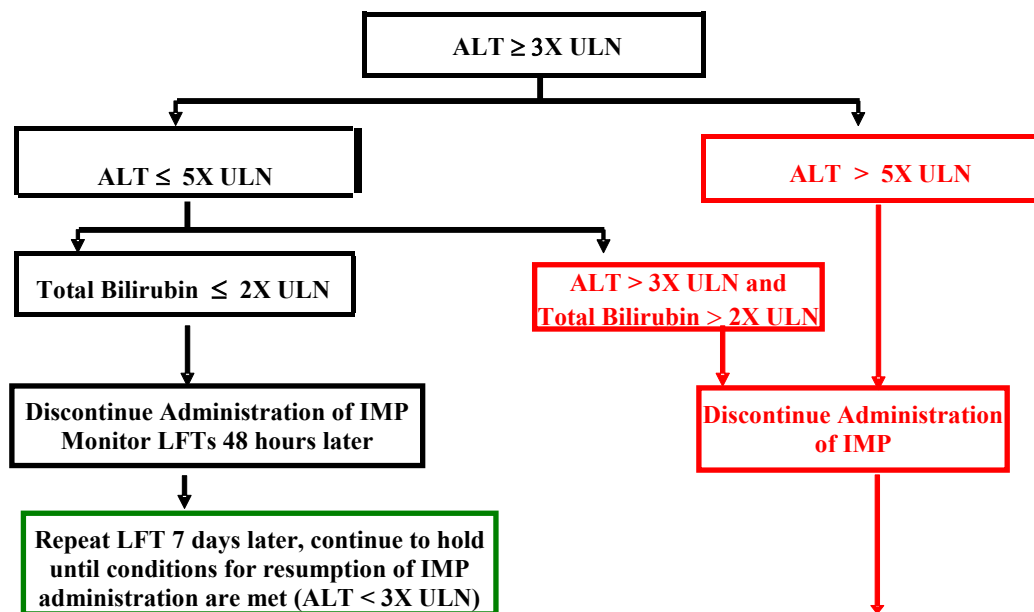


**Note:**

The procedures above flowchart are to be discussed with the patient only in case described in 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 adverse events in [Section 10.4.3](#) is met

ALT increase



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

## **Appendix F List of opportunistic infections**

- Aspergillosis
- Blastomyces dermatitidis (endemic in the south-eastern and south-central United 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 nontuberculosis mycobacteria
- Pneumocystis Carinii pneumonia (PCP)

This list is indicative and not exhaustive.



## Appendix G 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 a *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

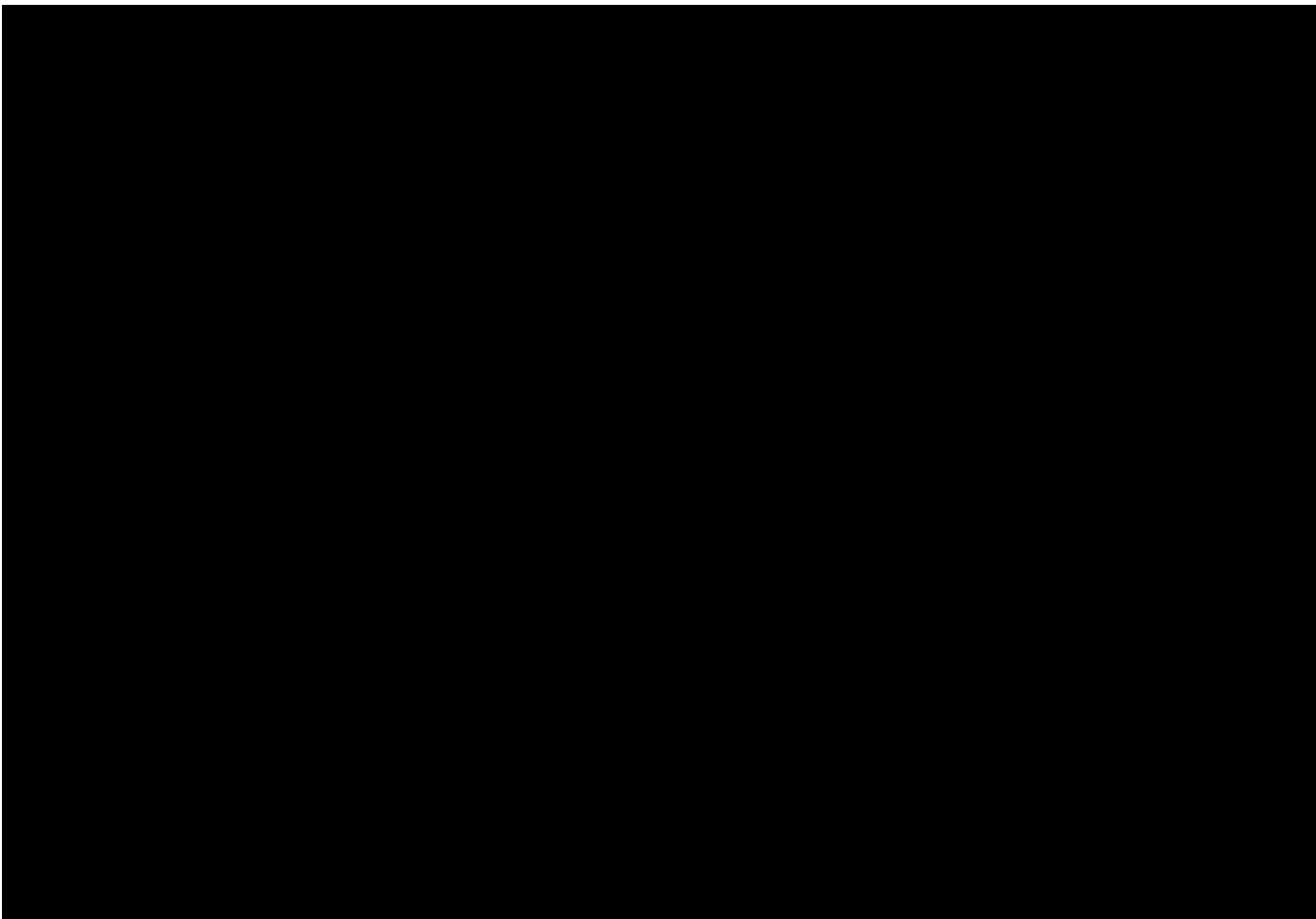
---

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.

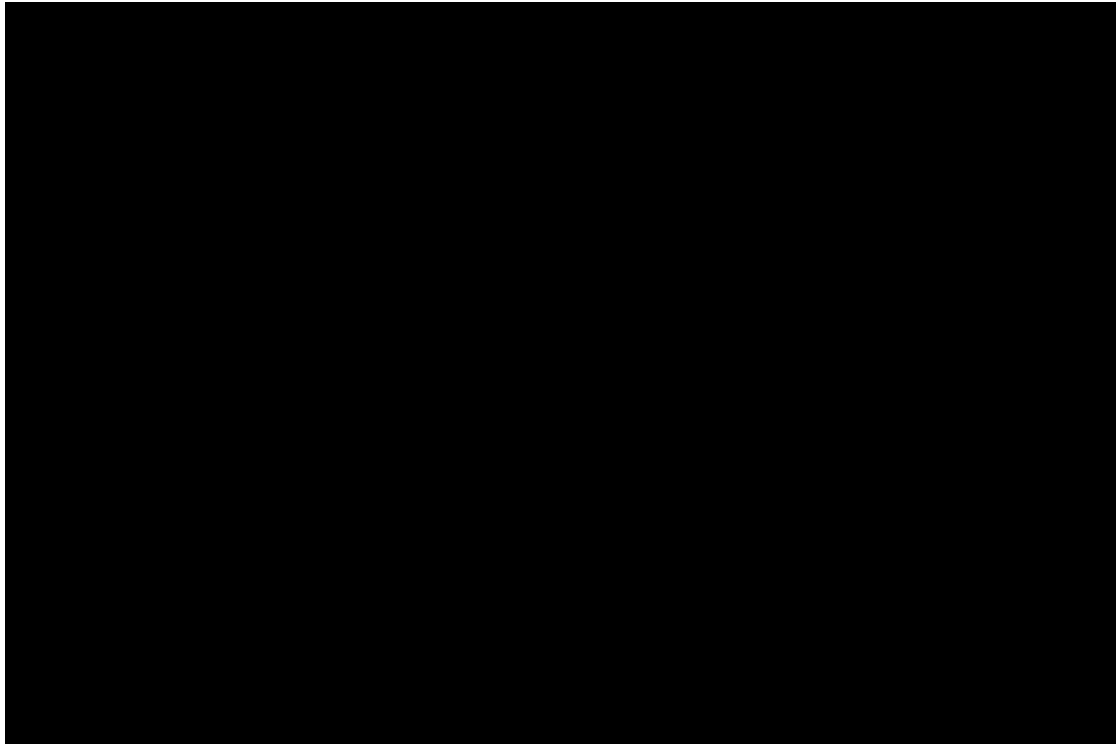
## **Appendix H FACIT- Fatigue (Paper Version)\***

FACIT-Fatigue Scale (Version 4), English (Universal) - Copyright 1987, 1997

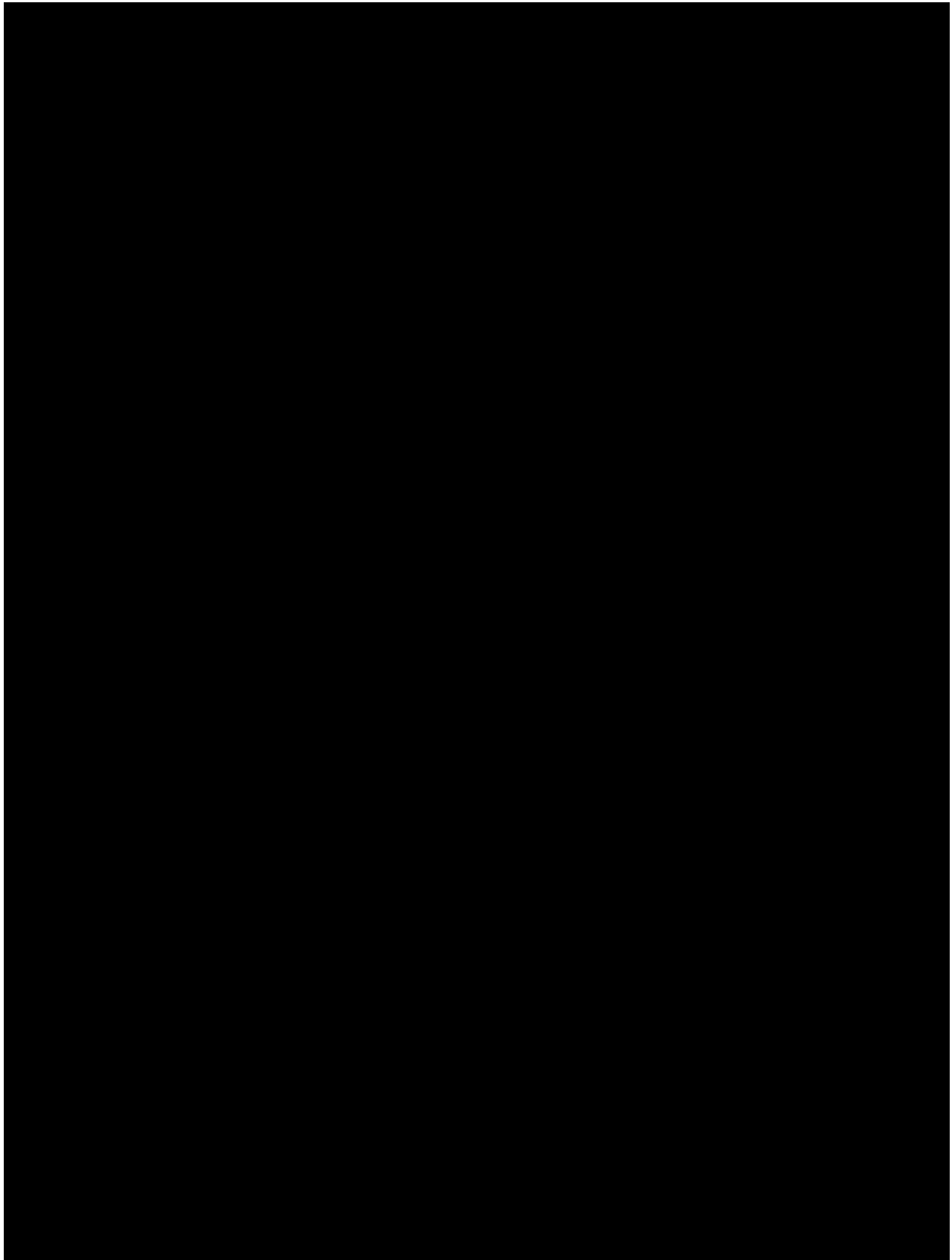


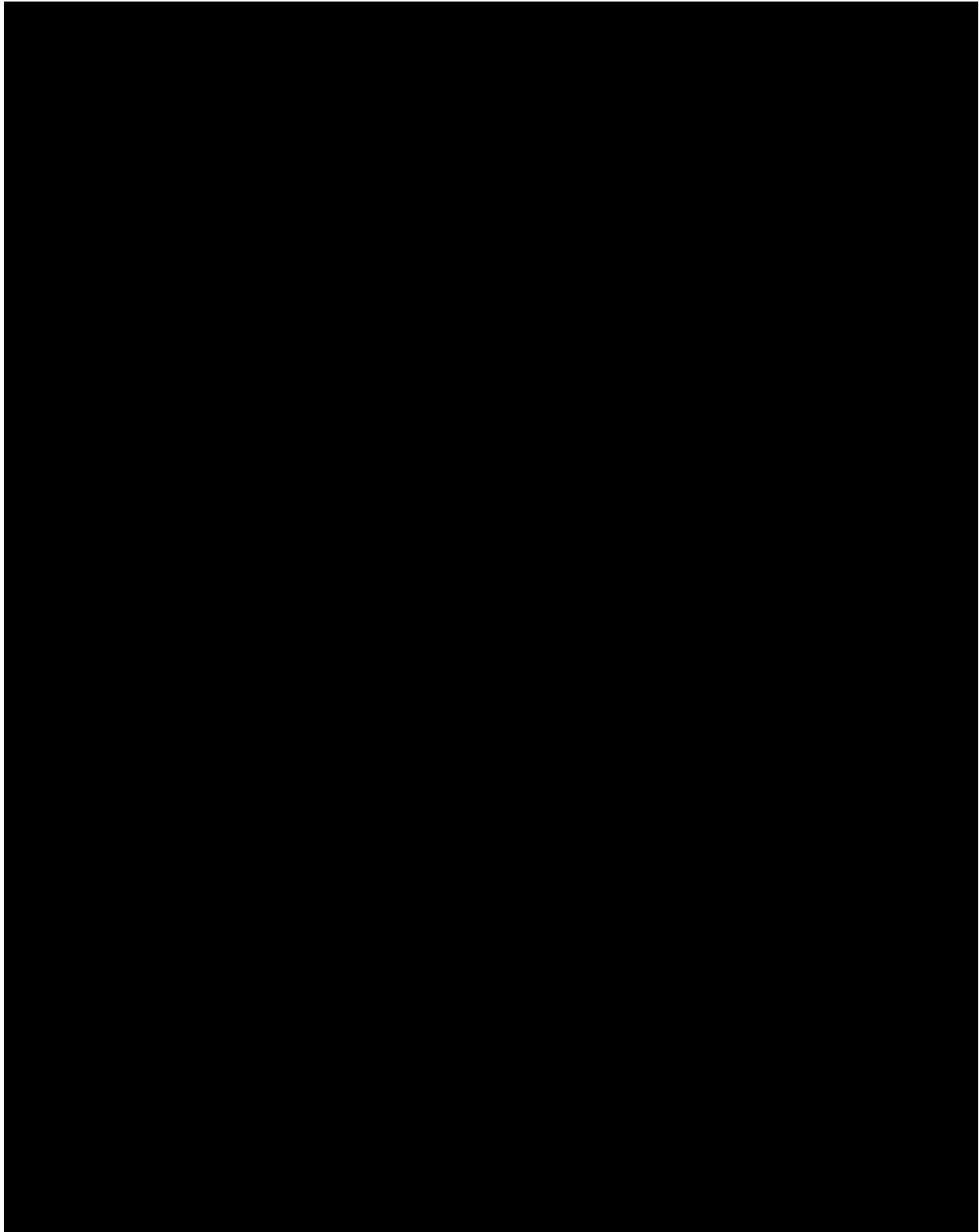
- \*This version will be adapted for use in the electronic format.

## Appendix I EuroQol Questionnaire (EQ-5D-3L) (Paper Version)\*



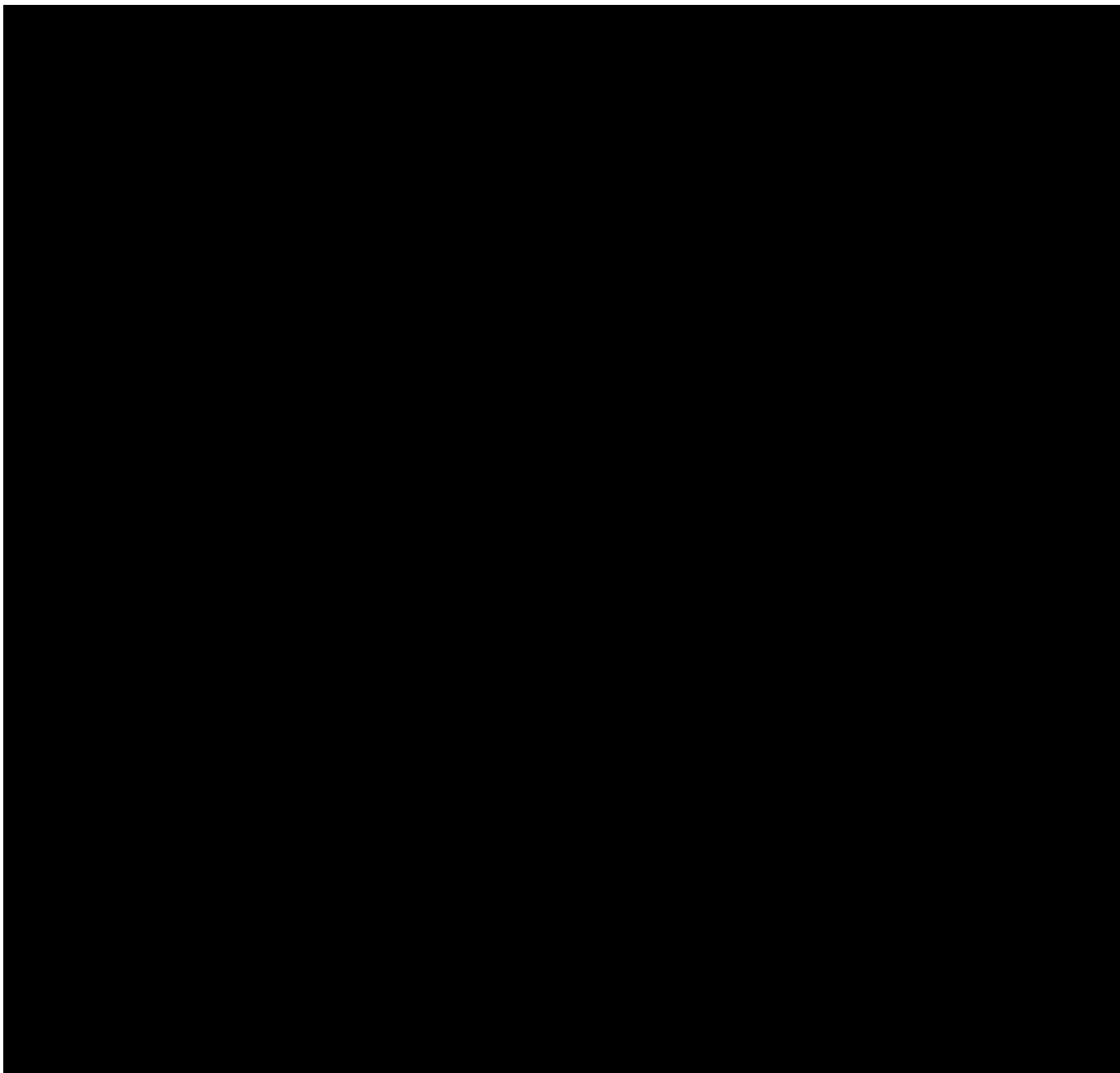
*US (English) © 1998 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group*

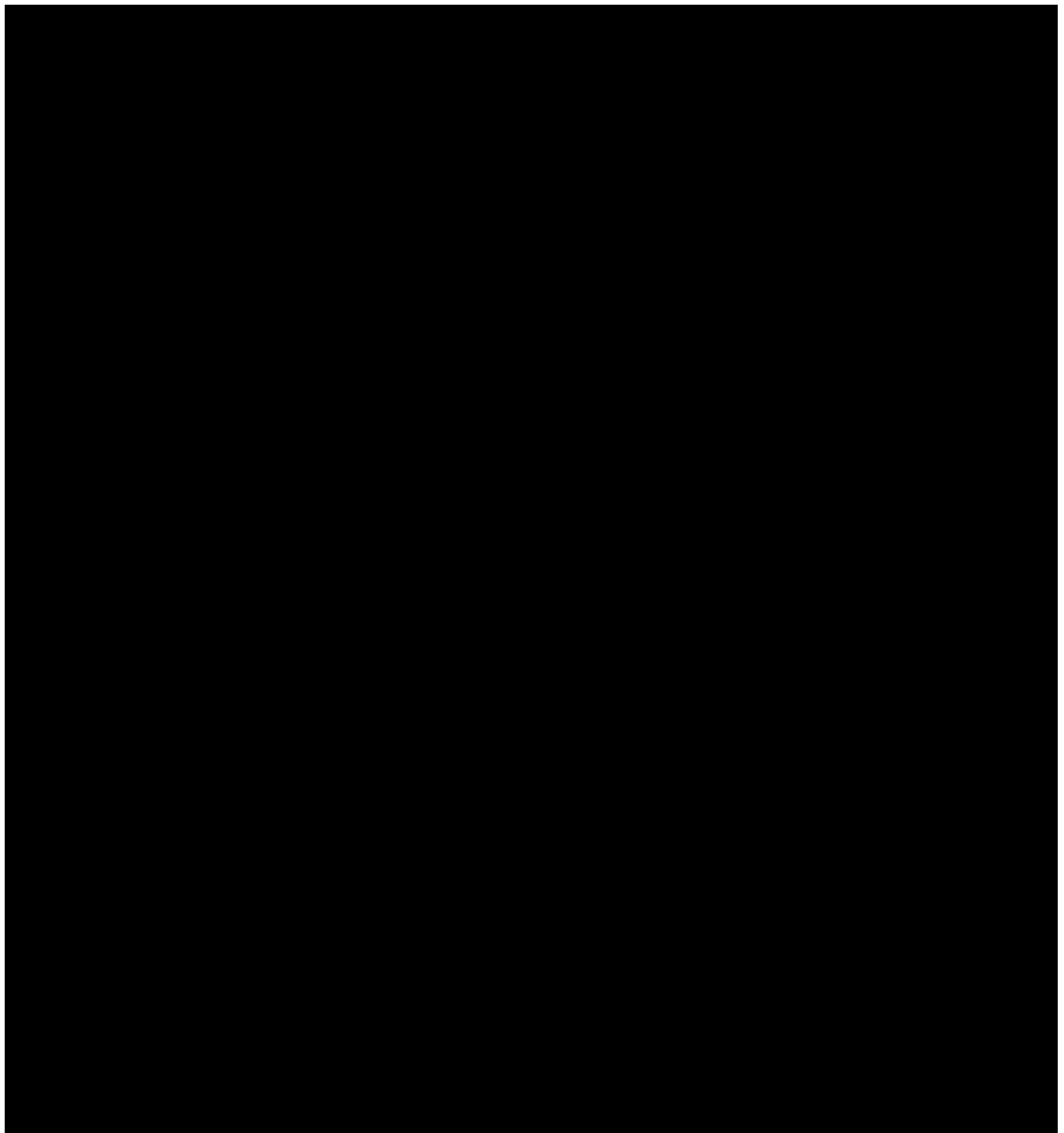


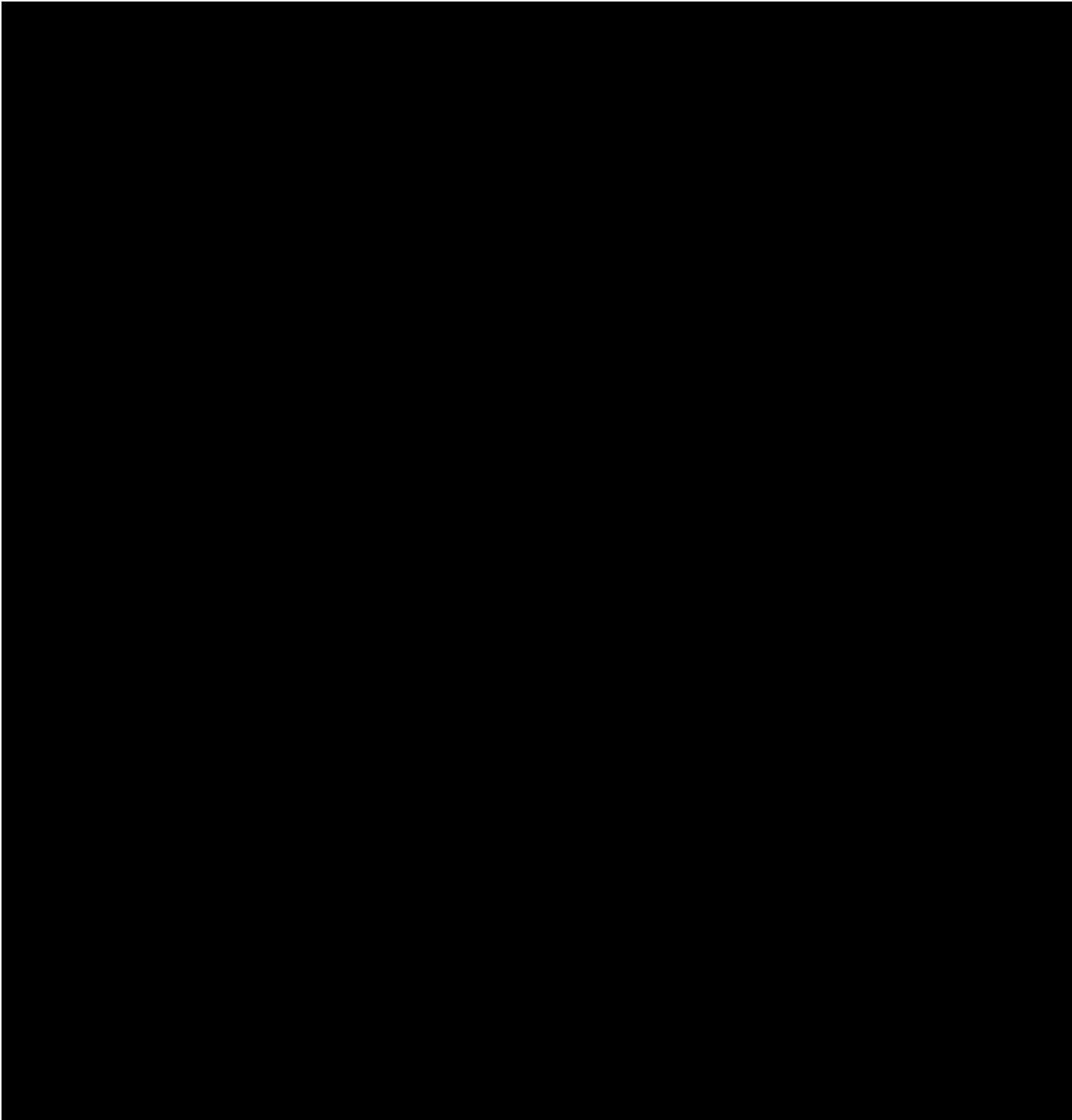


\*This version will be adapted for use in the electronic format.

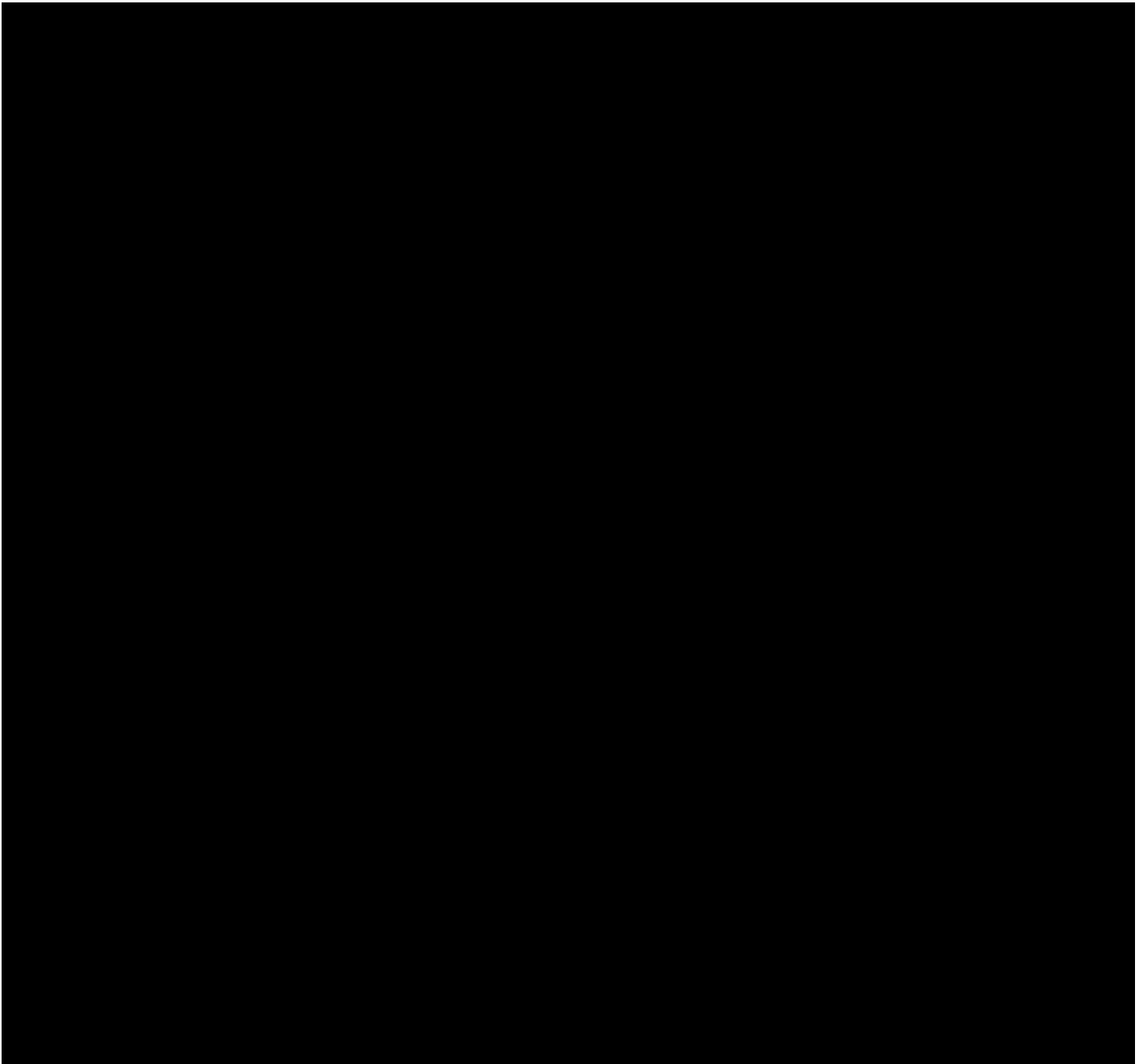
**Appendix J SF-36v2 (Paper Version)\***

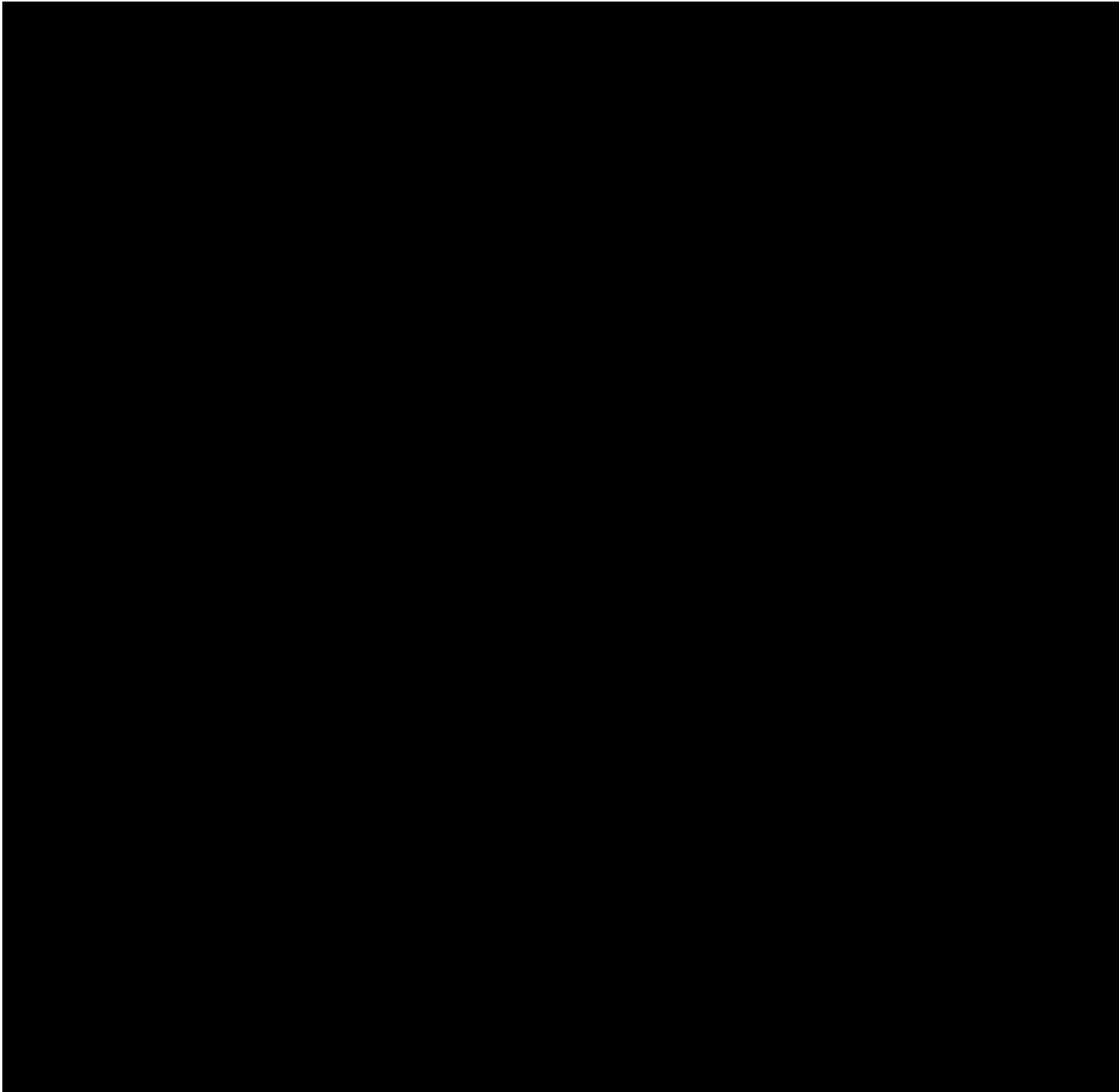


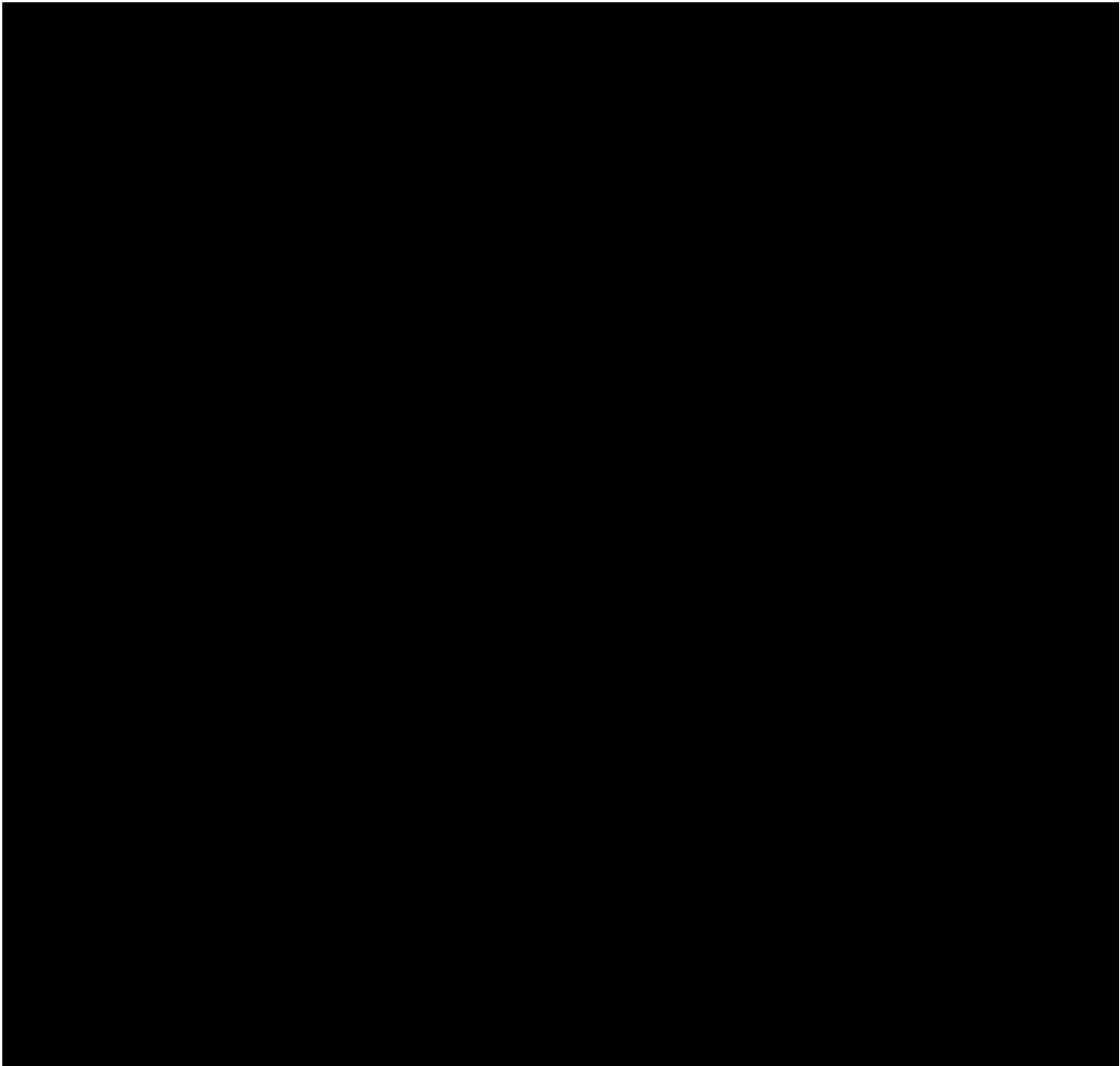












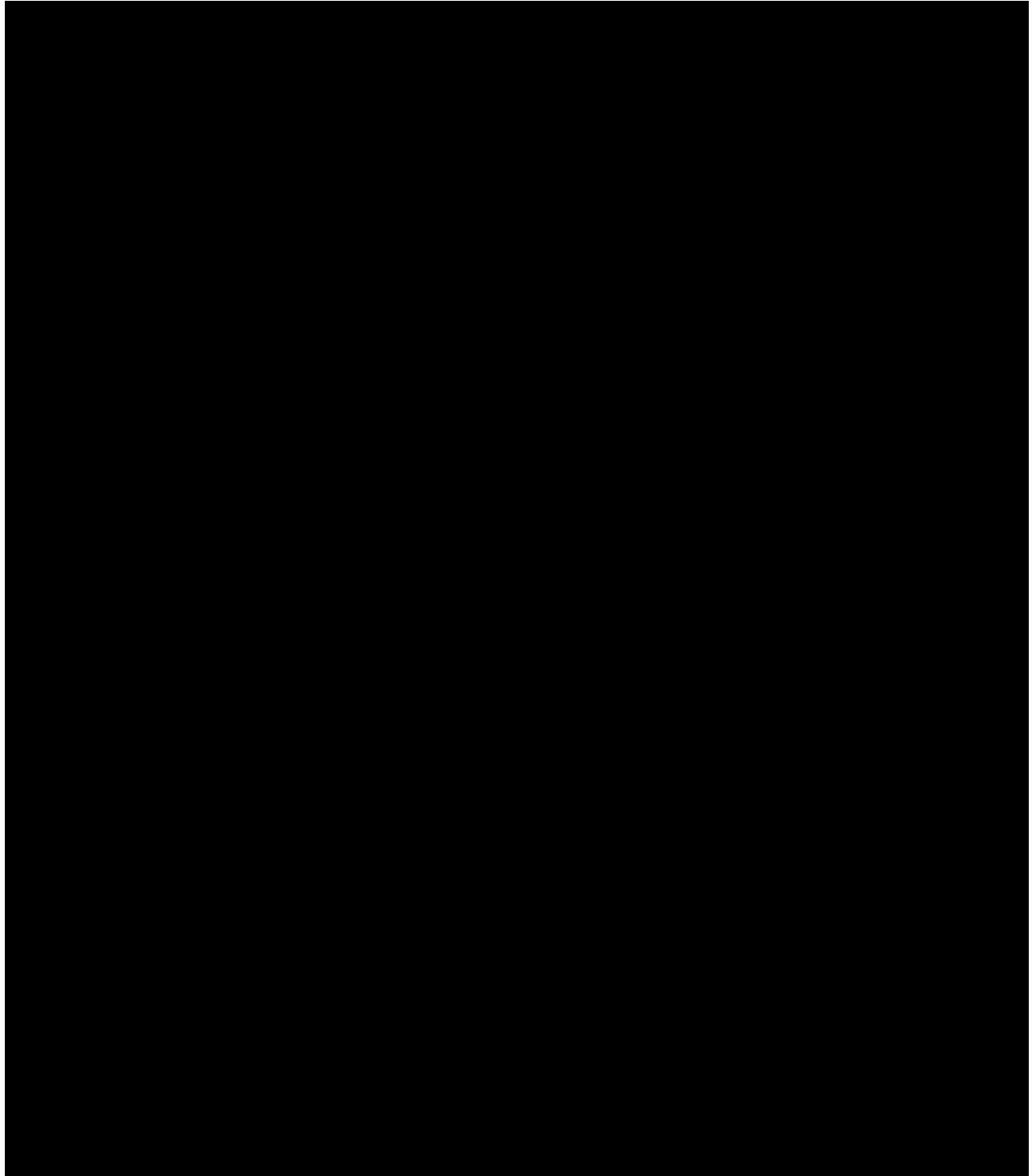
SF-36v2™ Health Survey © 1996, 2000 by QualityMetric Incorporated and Medical Outcomes Trust. All Rights Reserved.

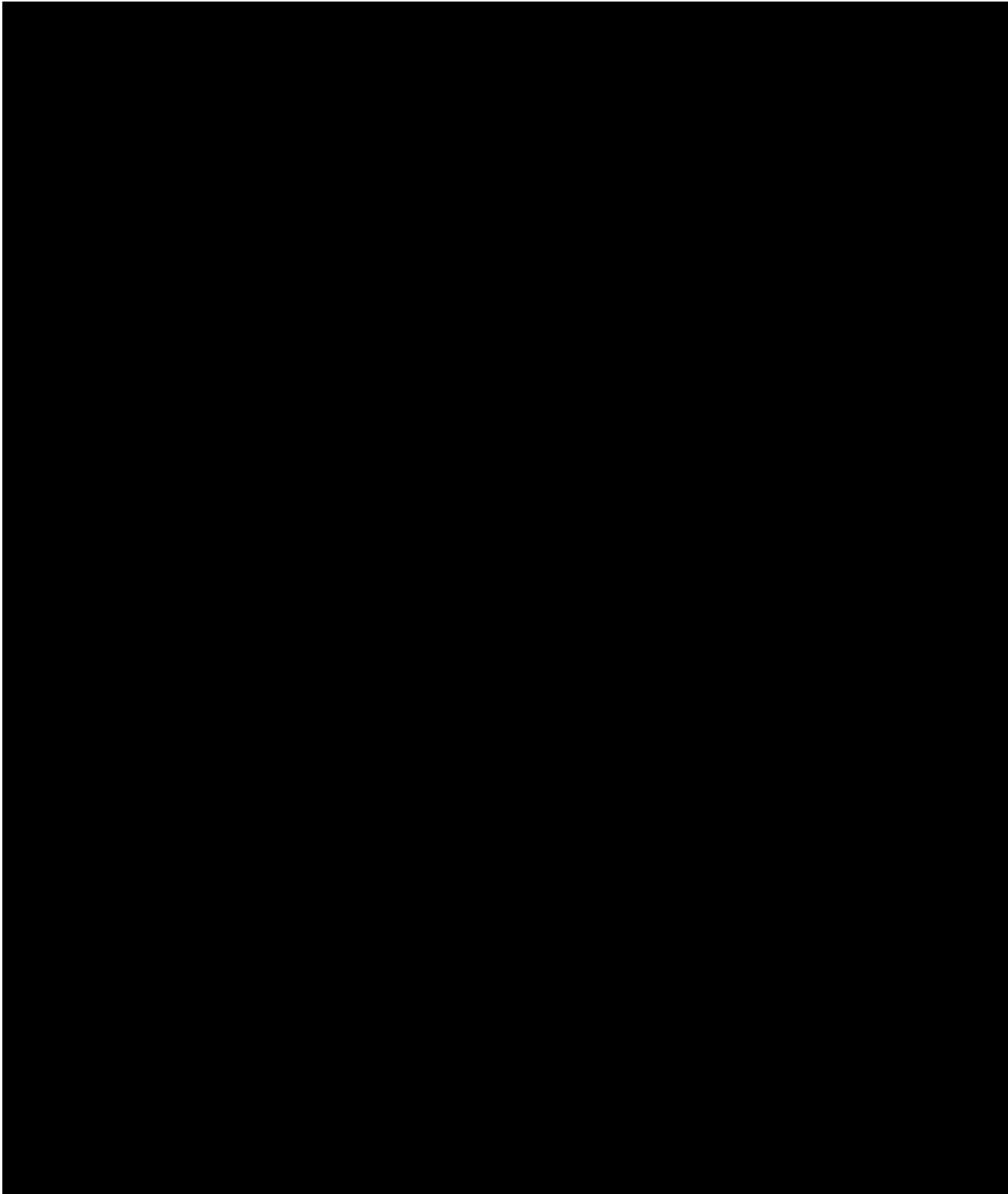
SF-36® is a registered trademark of Medical Outcomes Trust.

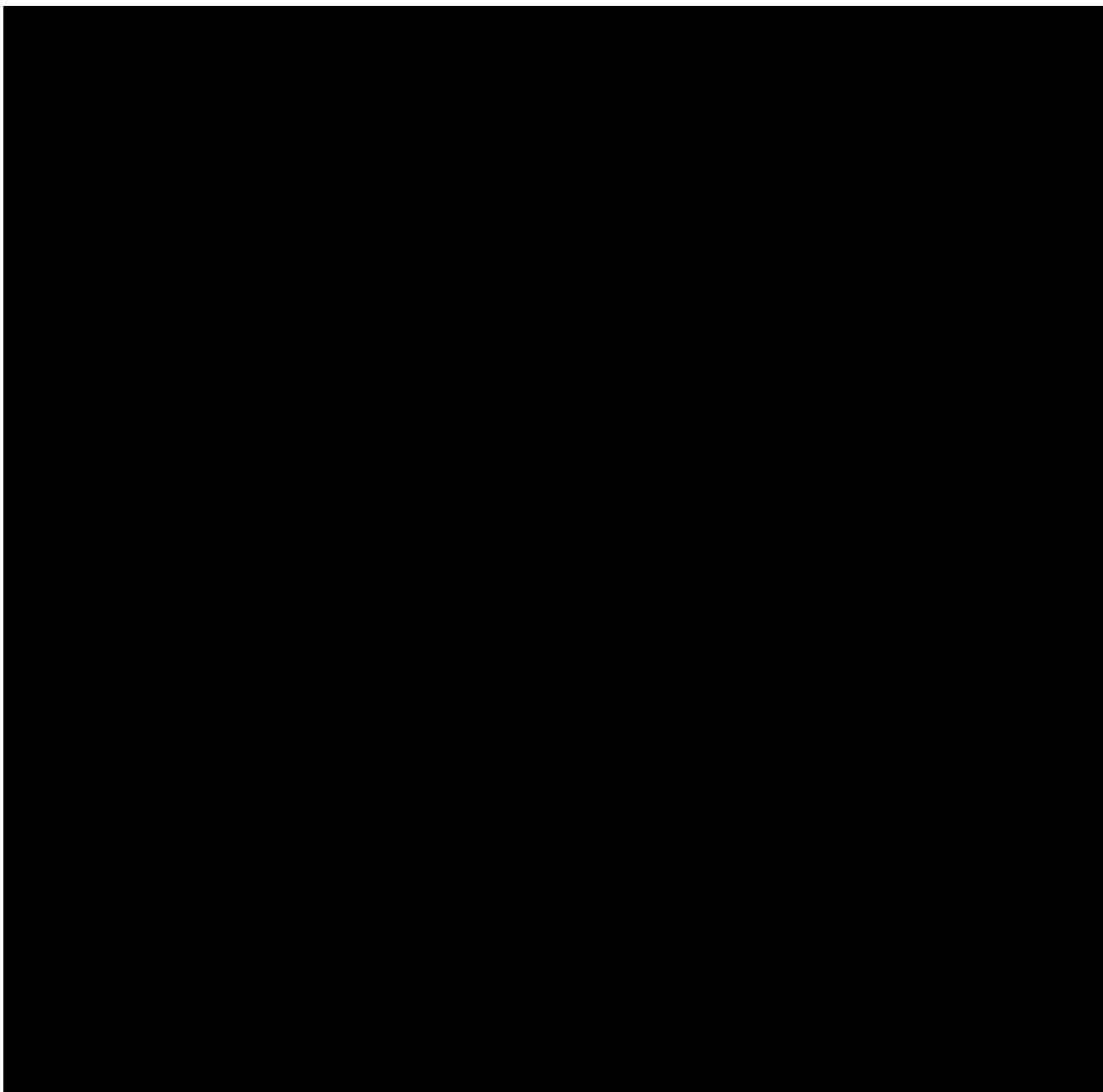
(SF-36v2 Standard, US Version 2.0)

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

## Appendix K HAQ-DI – Health Assessment Questionnaire (Paper Version)\*







## Appendix L 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

-----	
<b>Not active</b>	<b>Very active</b>
<b>0 mm</b>	<b>100 mm</b>

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

## Appendix M Biomarker Objectives

The objectives of the Precision Medicine Plan are to characterize the disease activity of PMR 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 cell types, circulating proteins, genetics and evaluation of gene expression changes in an optional sub study.

### *Whole blood for immunophenotyping of circulating immune cell types*

The contribution of the innate and adaptive immune systems to PMR disease activity and treatment response are not well understood. In order to better characterize alterations of the innate and adaptive immune system pre-dose and after steroid taper or sarilumab treatment, whole blood collections at pre-dose at V2, V4 and V9 are proposed to characterize T cell subsets that are purported to be dysregulated in PMR patients (CD8 cytotoxic lymphocytes) (23, 24, 25, 26) and (27) or cells that produce or are activated by IL6 signaling (monocytes (28) and Th17 cells, respectively). A total of 80 patients (40 patients/arm) will be selected at random by IRT for this blood sampling and subsequent analysis.

### *Optional Future Use Sample - Biomarker Serum and Plasma*

The purpose of storing serum and plasma is to analyze at a later time point proteins at baseline and after treatment that may be associated with disease progression of PMR and related diseases, severity and treatment response to anti IL-6R therapy. Although acute phase reactants have been well described in PMR patients, proteins that associate with PMR symptoms of morning stiffness and shoulder and hip pain have not been explored in the other studies. Proteins that may be explored include but not limited to the following: proteins involved in the IL6 signaling pathway (IL-6, soluble IL-6R, fibrinogen, serum amyloid A, synovitis and bursitis (adhesion and proteases (29, 30)), cytokines involved in TH1/Th17 pathway and the HPA axis (cortisol) (31, 32, 33).

### *Optional Pharmacogenetics substudy for DNA and RNA*

For the optional pharmacogenetics substudy, 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 pre-dose at V2 and then pre-dose 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. The DNA and RNA will be stored for up to 15 years from the completion of the clinical study report (CSR), or as otherwise required by local regulations. Specific procedures for collection, shipping and storage of pharmacogenetics samples will be provided in a separate manual. 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.

## Appendix N Protocol amendment history

### Amended protocol 01 (19 Sep 2018)

This amended protocol (amendment 01) is considered to be nonsubstantial 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 amendment 1 and amended protocol 01 (19 Sep 2018)

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**

<b>Section # and Name</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
Section 7.2.2 Exclusion Criterion 15	The initial wording of this criteria was modified with the elimination of, "Based on investigators' judgment," and addition of, "Patient who meets any of the following".	The modification was made based upon request from the European Regulatory Authorities. The underlying criterion has not changed.
Sections 10.4.1 and 10.4.3	Additional wording was added to both sections pertaining to ALT discontinuation criteria.	The modification was made based upon the recommendation from the European Regulatory Authorities to improve clarity. The underlying criteria in both sections have not changed.
Section 12.2	Language pertaining to the use of legal representative was modified.	The modification, made based upon an inquiry from the European Regulatory Authorities, explains the specific use of a legal representative that may be required for certain countries in obtaining the informed consent when a patient may be able to give consent but not able to sign the document.

Signature Page for VV-CLIN-0035553 v2.0  
efc15160-16-1-1-amended-protocol02

Approve & eSign	
-----------------	--

Approve & eSign	
-----------------	--