CLINICAL TRIAL PROTOCOL

COMPOUND: SAR153191 (sarilumab)

Effect of sarilumab on patient-reported outcomes in patients with moderately to severely active rheumatoid arthritis and with inadequate response or intolerance to current conventional synthetic DMARDs or tumor necrosis factor inhibitors

STUDY NUMBER: SARILL08755

SariPRO

Version Number:	3.0	EudraCT IND Number(s)	2017-002951-27 Not applicable
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CLINICAL TRIAL SUMMARY

COMPOUND: Sarilumab	**STUDY No.: SARILL08755** **STUDY NAME: SariPRO**
TITLE	Effect of sarilumab on patient-reported outcomes in patients with moderately to severely active rheumatoid arthritis and with inadequate response or intolerance to current conventional synthetic DMARDs or TNF inhibitors
INVESTIGATOR/TRIAL LOCATION	Mainland France
PHASE OF DEVELOPMENT	Phase IV
	STUDY OBJECTIVES
STUDY DESIGN	SariPRO is a national, multicenter, open-label, single-arm phase IV study. Four study periods are defined for this study period: • Screening period: within 28 days prior to study treatment start (Baseline visit, Day 1), patient eligibility is determined at the Screening visit. At Baseline visit, patient's inclusion in the study is established. • 6-month core period: patients who fulfil the enrollment criteria received a SC injection of sarilumab 200 mg every 2 weeks as monotherapy and/or in combination with methotrexate (MTX) or csDMARD(s) (at investigator's discretion) for 24 weeks. Patient visits are scheduled at W4, W12, and W24. • LTE period: all the patients who will complete the 6-month-core-period are allowed to continue the treatment with sarilumab, every 2 weeks for a maximum of another 24 weeks or until the commercial availability of sarilumab in France, depending whichever comes first. Patient visits are scheduled every 12 weeks over the LTE period (at W36 and W48). • Post-treatment follow-up: each patient will have one follow-up visit, between 2 and 4 weeks after his/her last administration of sarilumab.
STUDY POPULATION **Main selection criteria (6-month core period)**	**Inclusion criteria:** • Adult patients (≥18 years) with moderately to severely active RA according to the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) 2010 Rheumatoid Arthritis Classification Criteria • Patients with moderate to severe disease activity of

	RA defined as a DAS28-ESR >3.2 at Screening • Patients with inadequate response within at least the last 3 months or intolerance to current csDMARD or to at least one anti-TNF therapy (as defined by the investigator) • Oral corticosteroids (≤15 mg/day prednisone or equivalent) and NSAIDs or COX-2 (up to the maximum recommended dose) are allowed if at a stable dose for at least 4 weeks prior to Baseline • Permitted csDMARDs are allowed if at a stable dose for at least 4 weeks prior to Baseline • Females of childbearing potential can participate in this study only if using a reliable means of contraception during the study and for at least 3 months following the last dose of sarilumab • Female of childbearing potential must have a negative pregnancy test at the Screening and Baseline visits • Patients must have signed a written informed consent prior to perform any study-related procedures. **Exclusion criteria:** • Rheumatic autoimmune disease other than RA or prior history or current inflammatory joint disease other than RA • Treatment with any investigational agent within 4 weeks of Screening • Last RA treament prior to inclusion with any antiJAK or biologic DMARD other than anti-TNF • Patients treated with anti-TNF (e.i. adalimumab, infliximab, certolizumab, golimumab, etanercept) before the screening period, which are maintained within the 4 weeks before the inclusion (i.e.the first injection of sarilumab) • Intra-articular or parenteral corticosteroids within 4 weeks prior to Baseline • History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies (or to any of the excipients associated to sarilumab) • Stage III or IV cardiac failure according to the New York Heart Association classification • Evidence of active malignant disease, malignancies diagnosed within the previous 10 years (except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri previously excised and cured) • Patient who is institutionalized due to regulatory or legal order or patient who is mentally disabled or educationally disadvantaged • History of previous gastrointestinal perforation or diverticulitis • Known active current/ recurrent infections (including

	B and C hepatitis) NOTE: in case of latent TB infection the patient may be included if a subsequent appropriate anti TB treatment is initiated since at least 3 weeks • Active tuberculosis or history of incompletely treated tuberculosis • Evidence of serious uncontrolled concomitant disease, including severe uncontrolled hypercholesterolemia or hypertriglyceridemia at Screening • Hemoglobin <8.5 g/dL at Screening • Creatinine clearance <30 mL/min at Screening • White blood cells <3000/mm^3 at Screening • Absolute neutrophil count <2000/mm^3 at Screening • Absolute lymphocyte count <500/mm^3 at Screening • Platelet count <150 000 cells/mm^3 at Screening • AST or ALT >1.5 x ULN at Screening • Total bilirubin >ULN at Screening, unless Gilbert's disease has been determined by genetic testing and has been documented • Total fasting cholesterol >3.50 g/L [9.1 mmol/L]) or triglycerides >5.00 g/L [5.6 mmol/L]) at Screening.
Total expected number of patients	140 patients enrolled in 35 university hospitals and general hospitals centers are expected throughout mainland France.
STUDY TREATMENT(s)	
Investigational medicinal product(s)	Sarilumab, anti-IL6R mAb (anti-interleukin 6 receptor monoclonal antibody)
Formulation:	Single-use prefilled glass syringes of sarilumab 200 mg (and 150 mg in case of laboratory abnormalities)
Route(s) of administration:	Subcutaneous (SC) route, in abdomen, thigh, or upper arm
Dose regimen:	Sarilumab 200 mg is to be administered every 2 weeks (q2w) over the both treatment periods (as monotherapy or in combination with a csDMARD according to the investigator decision).
Non-investigational medicinal product(s)	NA
Formulation:	
Route(s) of administration:	
Dose regimen:	
Post-trial access to study medication	NA

ENDPOINTS	**Primary endpoint (6-month core period):** Change in the total RAID score from baseline to Week24 **Secondary efficacy endpoints (6-month core period):** • Values at each assessment visit and changes from baseline for the total RAID score, HADS, MAThys, FACIT-Fatigue, HAQ-DI, morning stiffness, International Physical Activity Questionnaire, and patient global assessment of disease activity • Values at each assessment visit and changes from baseline for ESR, DAS28-ESR, CDAI, and joint counts (TJC, SJC) • DAS28-ESR Low Disease Activity (LDA) and remission, CDAI LDA and remission, at W12 and W24 **Safety endpoints (6-month core and long-term extension periods):** • Incidence and severity of adverse events (AEs), serious and non-serious AEs, AESIs, AEs leading to dose modification or treatment withdrawal, AEs leading to death • Physical examination, vital signs, and clinically significant laboratory abnormalities over time.

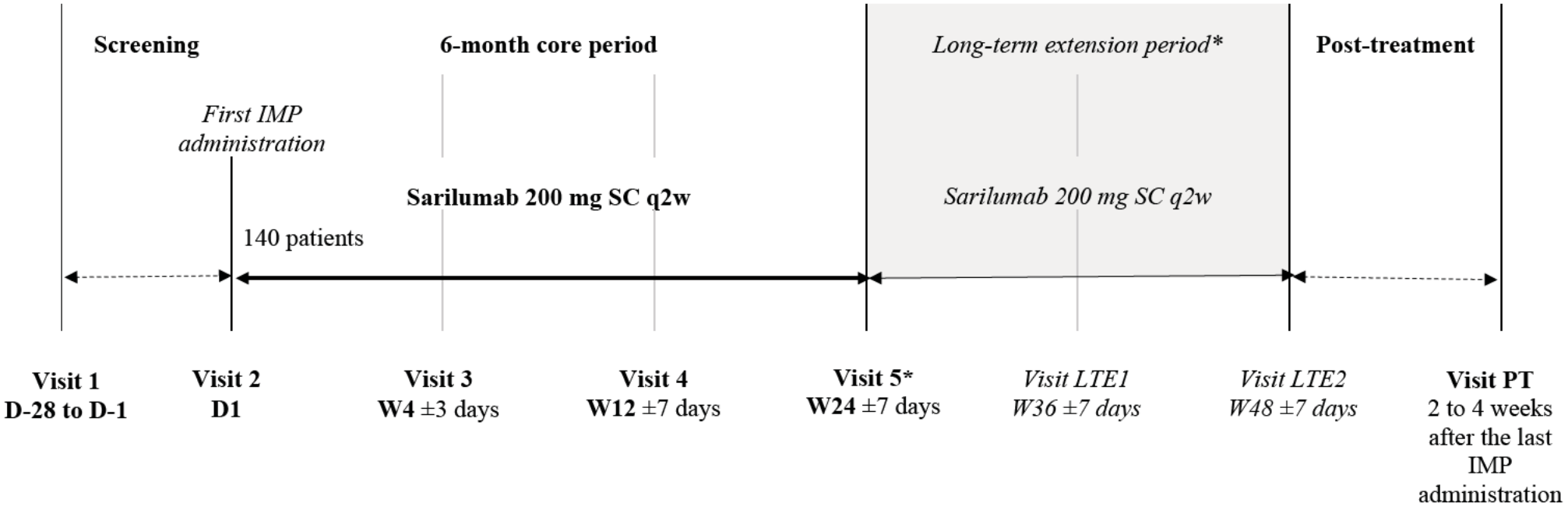
ASSESSMENT SCHEDULE	The study will consist of the following visits:
	• Visit 1 (D-28-D-1): screening
	• Visits of the 6-month core period:
	  • Visit 2 (D1): baseline, first sarilumab administration
	  • Visit 3 to 5 at W4, W12, and W24, respectively: on treatment
	• Visits of the LTE period (if applicable)
	  • Visits LTE 1 and LTE 2 at W36 and W48, respectively: on treatment
	• Visit PT: post treatment.
	At screening and at 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. For an overview of the local laboratory tests, see the study flowchart below, which include hematology, chemistry, and lipids. A serum pregnancy test for women of childbearing potential will be obtained at Screening as well.
	PROs (RAID, HADS, MAThyS, FACIT-Fatigue, HAQ-DI, duration of morning stiffness, IPAQ, and patient global assessment of disease activity) will be assessed (completed by patients before all other assessments performed during the 6-month core study visits) at Baseline, Week 4, Week 12, and Week 24, as well as efficacy assessments (ESR, DAS28-ESR, CDAI, and joint counts (TJC, SJC, on 28 joints for both counts).

	Safety assessments are performed at each assessment visit during the 6-month core period (and over the LTE period if applicable) and at the post-treatment visit. They include Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest including symptomatic overdose and pregnancy. Patients and Investigators must respect the visit schedule per study flowchart. If a visit date is changed, the next visit should take place according to the original schedule.
STATISTICAL CONSIDERATIONS	**Sample size determination:** According to the literature and previous studies having assessed sarilumab, the standard deviation (SD) of the RAID score could be estimated at 2.5 points. On this basis, a sample size of 140 included patients in order to have at least 112 evaluable patients (assuming almost 20% of non-evaluable patients), produces a precision, two-sided 95% confidence interval (CI), with a distance from the mean to the limits that will be less than 0.5 (considering 20% non-evaluable patients) when the estimated SD is 2.5, assuming that the change from baseline will be from 30% to 50% of baseline score. **Analysis populations:** • Intent-to-treat (ITT) population: all patients who met the eligibility criteria and who are actually treated. • Safety population: all patients who have signed the Informed Consent Form (ICF) and have been exposed to at least one dose or part of a dose of IMP. • Per-protocol population: patients of ITT population without major protocol deviations. **Primary analysis:** The primary study objective is to assess the change in RAID score from baseline to W24. The number of available data, mean, standard deviation, median and range (minimum, maximum) will be provided with the 95% confidence interval of the mean change from baseline to W24. Main analysis will be performed on ITT population. Sensitivity analysis will be conducted in reproducing the same analysis using the per-protocol population. In addition, multivariate analyses such as ANCOVA, Logistic Regressions and Multiple Correspondences analysis can be performed from baseline in order to exploratory explain patient profiles. **Analysis of secondary endpoints:** All secondary parameters will be described; 95% CI will be provided.

DURATION OF STUDY PERIOD (per patient)	The total duration of the core study period per patient is expected to be approximately 32 weeks: • Up to 4-week screening • 24 weeks treatment • 2-4 week post-treatment observations. For patients who will enter in the LTE period, a maximum of another 24 weeks is planned.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



** Patients who will complete the 6-month-core-period will be allowed to continue the treatment with sarilumab, every 2 weeks for a maximum of another 24 weeks or until the commercial availability of sarilumab, depending whichever comes first.*

1.2 STUDY FLOW CHART

	Screening	Treatment						Post-treatment observations	Early withdrawal
		6-month core period				*Long-term extension period*			
VISIT	V1	V2 (Baseline)	V3	V4	V5	*V LTE1*	*V LTE2*	V PT	
DAY / WEEK	D-28 to D-1	D1	W4 ±3D	W12 ±7D	W24 ±7D	*W36 ±7D*	*W48 ±7D*	2 to 4 weeks after the last IMP administration	
Eligibility									
Written Informed Consent	X								
Inclusion/Exclusion criteria	X	X							
Patient demography [a]	X								
Medical/surgical history	X								
Prior medication history	X								
Physical examination [b]	X				X				X
12-lead ECG and Chest X-ray [c]	X								
Treatment									
IMP administration [d]		←	—	—	→	←	→		
Concomitant medication review		X	X	X	X	*X*	*X*	X	X
Compliance / review patient diary			X	X	X	*X*	*X*	X	X
Patient Reported Outcomes									
RAID, HADS, MAThyS, FACIT-Fatigue, HAQ-DI, duration of morning stiffness, IPAQ, and patient global assessment of disease activity (VAS)		X	X	X	X				X
Efficacy									
ESR, DAS28-ESR, CDAI, and joint counts (TJC and SJC on 28 joints) [e]	X	X	X	X	X				X
Size of the largest rheumatoid nodule (if applicable)		X			X				X
Safety									
AE/SAE recording [f]		←	—	—	—	—	—	—	→
Vital signs [g]	X	X	X	X	X	*X*	*X*	X	X

Pregnancy test (for women of childbearing potential) [h]	X	X	X	X	X	X	X	X	X
Hematology [i]	D-7 to D-1		X	X	X	X	X		X
Serum chemistry [j]	D-7 to D-1		X	X	X	X	X		X
Serum iron, 25OHD [k]	X				X				X
Fasting lipids [l]	D-7 to D-1		X	X	X	X	X		X
Serology [m]	X								
Tuberculosis assessment [n]	X								

a) Gender and age.
b) A general physical examination should be performed during the Screening period (between D-28 and D-1). Body weight and waist circumference are to be recorded only at V2 and V5 (and at early withdrawal if applicable).
c) If at Baseline a chest X-ray has been taken within 90 days that shows no clinically significant abnormality, a further chest X-ray is not required. A 12-lead ECG should be performed during the Screening period.
d) Sarilumab 200 mg SC q2w, as monotherapy or in combination with a csDMARD (at Investigator's discretion). The first SC injection will be administered at the hospital site under supervision of the Investigator. For patients and/or non-professional caregivers able to perform SC injections at home, the investigator or delegate will provide training regarding the preparation and injections (at Baseline). For patients and/or non-professional caregivers completely unable to perform such injections at home, a home nursing will be needed.
e) Self-reported questionnaires should be completed by the patient before all other assessments performed during the study visits (and befoire the IMP administration if performed at this time).
f) All adverse events (date of onset, seriousness, maximum intensity, causal relationship with sarilumab, events leading to treatment modification or discontinuation, outcome of events).
g) Pulse rate, systolic and diastolic blood pressure (while seated).
h) Pregnancy tests will be locally conducted for female patients of child-bearing potential. Pregnancy test at Screening will be a serum test. All following pregnancy tests will be urine tests. If a urine test is positive it must be confirmed by a serum pregnancy test.
i) Hemoglobin, complete blood count (CBC), platelet count, and erythrocyte sedimentation rate (ESR) (blood should be drawn before drug administration). First tests will be performed during the 7-day period before inclusion. All tests will be performed locally.
j) Creatinine clearance, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (blood should be drawn before drug administration). First tests have to be performed during the 7-day period before inclusion. All tests will be performed locally.
k) Blood should be drawn before drug administration. First tests will be performed during the Screening period. All tests will be performed locally.
l) Total fasting cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides (blood should be drawn before drug administration). First tests have to be performed during the 7-day period before inclusion. All tests will be performed locally.
m) HBsAg, hepatitis B virus antibody and hepatitis C virus antibody will be performed during the Screening period only, unless clinically indicated during the trial.
n) If at Baseline a tuberculosis assessment (QUANTIFERON) has been taken within 90 days that shows no abnormality, a further QUANTIFERON test is not required. Further tuberculosis assessments are not required unless clinically indicated during the trial.

2 TABLE OF CONTENTS

LIST OF TABLES

3 LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
DME:	drug metabolizing enzymes
DTP:	direct-to-patient
ECG:	electrocardiogram
IEC:	independent ethics committee
IMP:	investigational medicinal product
INN:	international nonproprietary name
IRB:	institutional review board
IRT:	interactive response technology
NIMP:	noninvestigational medicinal product
PRO:	patient reported outcome
PV:	pharmacovigilance
SAE:	serious adverse event
WOCBP:	woman of child-bearing potential

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

4.1.1 Background on rheumatoid arthritis and treatments

Rheumatoid arthritis (RA) is a progressive, systemic autoimmune disease characterized by inflammation of the synovium leading to irreversible destruction and disability of the joints (1). The inflammatory process can also target other organs, characteristically bone marrow (anemia), eye (scleritis, episcleritis), lung (interstitial pneumonitis, pleuritis), cardiac (pericarditis) and skin (nodules, leukocytoclastic vasculitis).

It is estimated that approximately 0.5-1% of the adult population in North America and Europe is affected by RA (2) with 65-70% of RA patients having progressive disease that leads to joint destruction, disability and premature death (3, 4, 5). RA affects three times more women than men and the incidence is highest among women over 40 years of age (6).

Apart from symptomatic treatments as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) were shown to maintain or improve physical function and retard radiographic joint damage (7). More recently, biological compounds including those targeting tumor necrosis factor (TNF) alpha, B-cells, or T-cells, have been used successfully to treat RA, and demonstrate greater efficacy in combination with the reference csDMARD, methotrexate (MTX). However, about 30-40% of patients fail to respond to these therapies (8, 9) and 50-60% fail to achieve a major clinical response (by American College of Rheumatology [ACR] criteria or good response by European League Against Rheumatism [EULAR] criteria).

These limitations have prompted the development of therapies with alternative mechanisms of action. Interleukin 6 (IL-6) is a key cytokine involved in the RA pathogenesis causing inflammation and joint destruction (10, 11). Inhibition of IL-6 signaling through blockade of the IL-6 receptor (IL-6R) was first demonstrated to be effective by tocilizumab, a humanized monoclonal antibody (mAb) to the IL-6 receptor, with intravenous (IV) and newly subcutaneous (SC) formulations (12-18).

4.1.2 Sarilumab

Sarilumab, a fully human IgG1 mAb produced using a novel technology Velocimmune® developed by Regeneron, targets IL-6R and inhibits IL-6 signaling. Its binding affinity relative to tocilizumab is approximately 20-fold greater (19). Sarilumab has been developed for SC administration.

In combination with MTX or another csDMARDs, sarilumab demonstrated strong efficacy results compared to placebo, from previous pivotal phase III studies conducted by Sanofi and Regeneron (20, 21):

	MOBILITY (20) Sarilumab 200 mg q2w + MTX vs. placebo + MTX (n=399)	**TARGET** (21) Sarilumab 200 mg q2w + csDMARD vs. placebo + MTX (n=184)
ACR response at Week 24		
ACR20	66.4% vs. 33.4% *	60.9% vs. 33.7% *
ACR50	45.6% vs. 14.6% *	40.8% vs. 18.2% *
ACR70	24.8% vs. 7.3% *	16.3% vs. 7.2% *
HAQ-QI		
Mean change from baseline	-0.55 vs. -0.29 at week 16 *	-0.47 vs. -0.26 at week 12 **
DAS28-CRP at Week 24		
Low disease activity (≤3.2)	49.1% vs. 16.8% *	40.2% vs. 13.8% ***
Remission (<2.6)	34.1% vs. 10.1% *	28.8% vs. 7.2% ****

** p <0.0001; ** p=0.0004; *** nominal p <0.05; ****p <0.025*

At week 24, improvement was stronger in patients treated with sarilumab (200 mg q2w) as monotherapy than those receiving adalimumab (40 mg q2w) (21):

	MONARCH (21)	
	Sarilumab 200 mg q2w (n=184) vs. adalimumab 40 mg q2w (n=185)	*p value*
ACR response at Week 24		
ACR20	71.7% vs. 58.4%	0.0074
ACR50	45.7% vs. 29.7%	0.0017
ACR70	23.4% vs. 11.9%	0.0036
HAQ-QI		
Mean change from baseline at Week 24	-0.61 vs. -0.43	0.0037
DAS28-ESR at Week 24		
Mean change from baseline	-3.28 vs. -2.20	<0.0001
Remission (<2.6)	26.6 % vs. 7.0%	<0.0001

Based on data from previous clinical trials, the most frequent adverse reactions occurred under sarilumab treatment were consistent with previous biologic studies: infections, neutropenia, thrombocytopenia, elevation in lipids, transaminases increased, and injection site reactions; the most frequent serious adverse reactions were infections (23).

On the basis of previous development program, sarilumab (Kevzara®) was approved by the European Medicines Agency on 23 June 2017 for the treatment of moderate-to-severe active RA

in adult patients who responded inadequately or were intolerant to csDMARDs or biologic DMARDs (23).

Kevzara® is expected to be available commercially in the second half of 2018 in France.

4.1.3 Patient Reported Outcomes (PROs)

Although disease status has been globally improved in RA, and inflammation is better controlled since the wide access to biologics, there remain some unmet needs as identified by patients' residual patient burden of disease and comorbidities.

Over the last 20 years, there has been a growing interest for subjective data and patients' health care perception (self-reported health assessment, quality of life, and satisfaction with health care and medication), especially in chronic diseases. Apart from preventing joint destruction and disability in RA patients, treatments aim to provide them better health-related quality of life (24-26) which leads to assess patient's perspective on outcomes since it is often different from physician's perspective.

PRO incorporation into clinical practice and in research in RA is widely supported by international organizations and professional bodies including the European Patients' Academy on Therapeutic Innovations (EUPATI; http://www.patientsacademy.eu/index.php/en/) and the EULAR (25) in Europe, and the Patient-Centered Outcomes Research Institute (PCORI; http://www.pcori.org/research-results) and the ACR (27) in the United States; all of whom recognize the patients' unique position in providing direct feedback on their disease.

Regarding RA treatments, PROs include overall disease burden assessment measured by generic or specific patient self-reported questionnaires, which assess domains such as pain or physical function, but may also include anxiety/ depression, fatigue, sleep and physical activities (28, 29). Depression is the most frequent comorbidity in RA (30). Such outcomes are of utmost importance to patients (31). In fact, patients strive for what they consider to be remission, which is normalization of patients' lives which includes also normal social life, normal physical activities etc. Although not all outcomes appear similarly accessible to disease-modifying therapies or biologics; since mental well-being is multi-factorial, levels of efficacy on such outcomes would be useful information for both patients and caregivers, and could help guide prescriptions.

PROs were assessed in RA patients treated with sarilumab in previous phase III studies [in combination with MTX or other csDMARD (32, 33) and as monotherapy (21)] showing an improvement from baseline by week 24 in patient global assessment of disease activity, pain, Health assessment questionnaire disability index (HAQ-DI), Short Form-36 (SF-36) physical score, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).

The Rheumatoid Arthritis Impact of Disease (RAID) scale is a patient-derived score developed by EULAR a few years ago (29). This specific composite index comprises the seven most important dimensions (measured with a numerical rating scale from 0 to 10) shown as useful for the assessment of PROs in RA patients: pain, functional disability, fatigue, emotional and physical well-being, sleep disturbance, and coping (29, 34). The RAID was assessed in the

international MONARCH and TARGET trials (21, 33), with greater improvement under sarilumab compared to placebo, but findings were not conclusive due to adjustment for multiplicity of tests. Furthermore, these randomized trials were conducted with the usual caveats associated to patient selection and patient characteristics.

In addition, few data are available regarding PROs in French RA patients (29, 35, 36). In particular, no French patients were included in the recent interventional comparative study aiming to assess PROs (including the RAID scale) in RA patients receiving sarilumab or placebo in combination or not with csDMARD (21, 33). Thus, knowing that the Outcome Measures in rheumatology (OMERACT) Equity Working Group suggested some heterogeneity in the PROs according to population characteristics (37), detection for PRO improvement is currently an important meaning for France besides efficacy criteria.

4.2 STUDY RATIONALE

This French study will permit data collection from an moderately to severely active RA patient population with the aim to analyze relevant data derived from PRO instruments in order to gain further insights into efficacy of sarilumab. This is all the more important given that some PROs domains were previously scarcely collected while being of great importance for RA patients. Furthermore they must be taken into account in the shared decision-making process for RA treatment (38).

More specifically, the main objective of this French single-arm, open-label phase IV study is to assess the effect of sarilumab on PROs including important but previously little assessed domains in particular in France, in patients with moderately to severely active RA and inadequate response or intolerance to current csDMARDs or TNF inhibitors.

Among all the studied PROs [RAID, Hospital Anxiety and Depression Scale, HADS (39); FACIT-F (40); HAQ-DI (41); International Physical Activity Questionnaire, IPAQ (42); Multidimensional Assessment of Thymic States, MAThyS (43), and patient global assessment of disease activity], RAID change from baseline to week 24 is chosen as primary criterion as this scale comprises the seven most important dimensions shown as useful for the PRO assessment in RA patients (29, 34).

Included patients will receive SC sarilumab 200 mg q2w, in accordance with the Summary of Product Characteristics (23). In addition to the efficacy of the product as previously shown, this limited number of injections, as done in this phase IV study with patient management closer to real-life clinical practice than in previous international clinical trials, may lead to provide a positive impact on patients' perceptions, and then to PROs improvement under treatment.

The 6-month-core period of the SariPRO study will be completed by another maximum 24-week period to assess long-term safety of sarilumab and to allow patients to pursue their treatment until sarilumab is commercially available in France.

5 STUDY OBJECTIVES

5.1 PRIMARY (6-MONTH CORE PERIOD)

The primary objective of this study is to describe the evolution of the perception of patients regarding the effect of sarilumab in combination with conventional synthetic Disease-Modifying Anti-Rheumatic Drug (csDMARD) and/or monotherapy on patient-reported impact of disease, using the rheumatoid arthritis impact of disease (RAID) questionnaire, in patients with moderately to severely active RA and inadequate response or intolerance to current csDMARD or TNF inhibitors.

5.2 SECONDARY (6-MONTH CORE PERIOD)

- To assess the change of the RAID score from baseline (to W4, W12, and W24) in patients with moderately to severely active RA and inadequate response or intolerance to current csDMARD or TNF inhibitors, treated with sarilumab in combination with csDMARD and/or monotherapy.
- To assess the effect of sarilumab in combination with csDMARD and/or monotherapy on other patient-reported outcomes (global assessment of disease activity, disability, morning stiffness, fatigue, anxiety/ depression, mood disorders, and physical activities), in patients with moderately to severely active RA and inadequate response or intolerance to current csDMARD or TNF inhibitors.
- To assess the efficacy of sarilumab in combination with csDMARD and/or monotherapy using DAS28-ESR and CDAI in patients with moderately to severely active RA and inadequate response or intolerance to current csDMARD or TNF inhibitors.
- To assess the safety of sarilumab in combination with csDMARD and/or monotherapy in patients with moderately to severely active RA and inadequate response or intolerance to current csDMARD or TNF inhibitors.

5.3 EXPLORATORY

- **Over the 6-month core period**
  - To describe the associations between changes in RAID score and composite disease activity scores (DAS28-ESR and CDAI).
  - To describe the associations between changes in HADS score and in composite disease activity scores (DAS28-ESR and CDAI)
  - To explore patient profiles (using multivariate method such as multiple correspondences analysis).
- **Over the long-term extension period (maximum 24 weeks)**

- To assess the safety of sarilumab in combination with csDMARD and/or monotherapy in patients with moderately to severely active RA and inadequate response or intolerance to current csDMARD or TNF inhibitors over the LTE period.

All other analyses that could give interesting information with respect of study objectives will be performed after agreement of the Scientific Committee of the study.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a national, multicenter, open-label, single-arm phase IV study designed to assess the effect of sarilumab on patient-reported impact of disease, using the rheumatoid arthritis impact of disease (RAID) questionnaire, in patients with moderately to severely active RA and inadequate response or intolerance to current csDMARD or TNF inhibitors.

Four study periods are defined for this study:

- Screening period: within 28 days prior to study treatment start (Baseline visit, Day 1), out-patient eligibility is determined at the Screening visit. At Baseline visit, patient's inclusion in the study will be established.
- 6-month core period: patients who fulfil the enrolment criteria will start the investigational medicinal product (IMP), SC injection of sarilumab 200 mg every 2 weeks as monotherapy and/or in combination with methotrexate (MTX) or other csDMARD (at investigator's discretion) for 24 weeks. Patient visits are scheduled at Baseline, W4, W12, and W24.
- Long-term extension period: all patients who will complete the 6-month-core-period will be allowed to continue the treatment with sarilumab, every 2 weeks for a maximum of another 24 weeks or until the commercial availability of sarilumab, depending whichever comes first. Patient visits are scheduled every 12 weeks over the LTE period (at W36 and W48).
- Post-treatment follow-up: each patient will have one follow-up visit, between 2 and 4 weeks after his/her last administration of sarilumab.

Around 140 patients enrolled in 35 university hospital and general hospital centers are expected throughout mainland France.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The total duration of the 6-month core study period per patient is expected to be approximately 32 weeks:

- Up to 4-week for screening
- 24 weeks for the treatment period (sarilumab 200 mg q2w)
- Between 2 and 4 week for post-treatment observations.

For patients who will enter in the LTE period, a maximum of another 24 weeks is planned.

6.2.2 Determination of end of clinical trial (all patients)

The end of the clinical trial in all participating sites is reached when the last patient last visit is completed per protocol. The last patient last visit will occur 2 to 4 weeks after the last sarilumab administration (i.e. at between Week 26 and Week 28 for patients who will not enter the LTE study and between Week 50 and Week 52 at a maximum for patients who will enter the LTE study).

6.3 INTERIM ANALYSIS

No interim analysis is planned.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA (6-MONTH CORE PERIOD)

I 01. Patient with moderately to severely active RA according to the 2010 EULAR/ACR criteria (see Appendix A)

I 02. Patient with moderate to severe disease activity defined as a DAS28-ESR >3.2 at Screening

I 03. Patient with inadequate response within at least the last 3 months or intolerance to current csDMARD or to at least one anti-TNF therapy (as defined by the investigator)

I 04. Oral corticosteroids (≤15 mg/day prednisone or equivalent) and non-steroidal anti-inflammatory drugs (NSAID) and cyclo-oxygenase-2 inhibitors (COX-2) (up to the maximum recommended dose) are allowed if at a stable dose for at least 4 weeks prior to Baseline

I 05. Permitted csDMARDs are allowed if at a stable dose for at least 4 weeks prior to Baseline

I 06. Patient able and willing to give written informed consent and to comply with the requirements of the study protocol.

7.2 EXCLUSION CRITERIA (6-MONTH CORE PERIOD)

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 two subsections.

7.2.1 Exclusion criteria related to study methodology

E 01. <18 years of age

E 02. Patient unable to understand and write adequately to complete the study PRO assessments

E 03. Exposure to sarilumab at any time prior to Baseline

E 04. Use of intra-articular or parenteral corticosteroids within 4 weeks prior to Baseline

E 05. Treatment with any investigational agent within the 4 weeks of Screening

E 06. Last RA treament prior to inclusion with any antiJAK or biologic DMARD other than anti-TNF

E 07. Patients treated with anti-TNF (e.i. adalimumab, infliximab, certolizumab, golimumab, etanercept) before the screening period, which are maintained within the 4 weeks before the inclusion (i.e.the first injection of sarilumab)

E 08. Rheumatic autoimmune disease other than RA or prior history or current inflammatory joint disease other than RA

E 09. Evidence of active malignant disease, malignancies diagnosed within the previous 10 years (except basal and squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri previously excised and cured)

E 10. Patient who is institutionalized due to regulatory or legal order or patient who is mentally disabled or educationally disadvantaged

7.2.2 Exclusion criteria related to the current knowledge of Sanofi compound

E 11. Pregnant or breastfeeding woman

E 12. Women of childbearing potential not protected by highly-effective contraceptive method(s) of birth control (as defined in the informed consent form and/or in a local protocol addendum/amendment) over the study period and for at least 3 months following the last dose of sarilumab, and/or who are unwilling or unable to be tested for pregnancy

E 13. History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies (or to any of the excipients associated to sarilumab)

E 14. Immunization with a live/attenuated vaccine within 4 weeks prior to Baseline

E 15. Stage III or IV cardiac failure according to the New York Heart Association classification

E 16. History of previous gastrointestinal perforation or diverticulitis

E 17. Known active current/ recurrent infections (including but not limited to active tuberculosis [TB] or history of incompletely treated TB and atypical mycobacterial disease, hepatitis B and C, and herpes zoster)

NOTE: in case of latent TB infection the patient may be included if a subsequent appropriate anti TB treatment is initiated since at least 3 weeks

E 18. Positive hepatitis B surface antigen (HbsAg), and/or positive total hepatitis B core antibody, and/or positive hepatitis C antibody (HCV) at the Screening visit

E 19. Evidence of serious uncontrolled concomitant disease, including severe uncontrolled hypercholesterolemia or hypertriglyceridemia

E 20. Patients with any of the following laboratory abnormalities at the Screening or Baseline visit:

- Hemoglobin <8.5 g/dL
- White blood cells <3000/mm^3
- Absolute neutrophil count <2000/mm^3
- Absolute lymphocyte count <500/mm^3
- Platelet count <150 000 cells/mm^3
- Creatinine clearance <30 mL/min
- AST or ALT >1.5 x ULN.
- Bilirubin (total) >ULN, unless Gilbert's disease has been determined by genetic testing and has been documented
- Total fasting cholesterol >3.50 g/L [9.1 mmol/L]) or triglycerides >5.00 g/L [5.6 mmol/L])

7.3 SELECTION CRITERIA (LTE PERIOD)

All the patients who will complete the 6-month-core period will be allowed to enter the LTE period, if sarilumab is not yet commercially available in France (as monotherapy or in combination with csDMARDs).

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

The investigational medicinal product (IMP) is sarilumab (Kevzara®) that is expected to be available commercially in the second half of 2018 in France.

Sarilumab will be supplied by the Sponsor in 1.14 mL ready-to-use, single-use prefilled glass syringes delivering 200 mg (175 mg/mL) of sarilumab for subcutaneous (SC) injections. A patient will use one prefilled syringe for each dosing. In case of specific laboratory abnormalities over the treatment period (see section 10.4.6 for more details), the Sponsor will supply 1.14 mL ready-to-use, single-use prefilled glass syringes delivering 150 mg (131.6 mg/mL) of sarilumab for SC injections, using the Intreractive Voice Response System (IVRS).

During the treatment period, the IMP should be administered every 14 days; however an IMP administration window of ±3 days is permitted per protocol to accommodate exceptional circumstances, eg, laboratory test result pending), ongoing adverse event, or patient scheduling difficulty.

Patients and/or their non-professional caregivers will be trained to administer IMP at the start of the treatment period. This training must be documented in the patients' study file. The study coordinator or designee may administer the first injection, or allows the patient to self-inject, under observation, and provide feedback on technique, thus combining the initial dose administration as part of the training procedure on Treatment Period Day 1 (Visit 2). If SC injections have to be done on days when the patient has a study visit, the IMP will be administered following clinic procedures and blood collection. For doses not given at the study site, a diary card will be provided to record information pertaining to these injections; these diaries will be kept as source data in the patients' study file.

If a patient or non-professional caregiver is completely unable to administer sarilumab at home, it is permitted that the dose will be administered as described above by a home nurse as scheduled.

Sarilumab is administered as subcutaneous injection in the abdomen (except for the 2-inch area surrounding the navel), the front of the thigh or in upper arm. The site for each injection should be rotated. Injections should not be administered into skin that is sore (tender), bruised, red, hard, scarred or damaged. The injection sites will be inspected by the site personnel at each visit and any injection site reactions (ISRs) should be documented appropriately on the AE electronic Case Report Form (eCRF) page.

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCT(S)

Not applicable.

8.3 BLINDING PROCEDURES

Not applicable.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Not applicable.

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. In particular, study drug packaging will be overseen by the Sponsor clinical trial supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The primary treatment supply shall contain two kits of one prefilled syringe per patient in each, the first for the IMP injection at the inclusion visit and the second for the second injection to be done at home. Following kits of one prefilled syringe will be provided for each patient, using the IVRS.

Additional treatment kits to provide medication under circumstances as damaged kit or unusable kit will be allocated by IVRS.

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.

All sarilumab PFS must be stored at a controlled temperature of 2-8°C (with no freezing), and in the original carton in order to protect from light. After removing the PFS from the refrigerator, it should be allowed to warm up at room temperature before injecting sarilumab (for at least 30 minutes before using), and it should be administered within 14 days and should not be stored above 25ºC.

8.7 RESPONSIBILITIES

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

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

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

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 patients enrolled in the study), 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 (e-CRF) page for accounting purposes.
- A diary card will be provided to patients to record home injections. Patients will be asked to return all empty drug supply boxes, unused PFS, and diary cards to the clinic at each visit as a measure of drug accountability and patient compliance. Sharps containers for any used PFS will be provided locally to patients for home usage. After home injections, the used syringes must be placed into the sharps containers immediately. The sharps containers should be returned to sites and discarded by the site staff at the frequency per local schedule. So, sharps containers for used syringes, back-pack and insulated cooling bag for transport from sites to patient’s home will be provided by the sponsor to the site for the patients.
- The study coordinator tracks treatment accountability/compliance, either by diary, or by counting the number of unused/used treatment kits 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 partially used or unused treatments will be retrieved by the Sponsor or destroyed at study site.

A detailed treatment log of the returned/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 unused IMP unless the Sponsor provides written authorization. In this case, written documentation of destruction must contain the following:

- Identity (kit or packaging numbers and subject numbers) of IMP destroyed
- Quantity of IMP destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person who destroyed IMP.

In case of PFS failure, or if there are any issues with the drug, the syringe should not be destroyed, and instead should be returned to the appropriate Sponsor clinical trial supplies department for further assessment.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s). Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to Screening to the study completion/early termination visit. All concomitant medications should be reported to the Investigator and recorded on the corresponding pages of the patient e-CRF, along with a description of the type of drug or procedure, the amount, duration, reason for administration of drug, and the outcome of any procedure.

8.8.1 Prohibited medications

The use of any **biologic DMARDs**, including but not limited to etanercept, infliximab, anakinra, rituximab, abatacept, tocilizumab, certolizumab, golimumab, adalimumab and any **targeted synthetic DMARDs** such as tofacitinib, as well as any biologic DMARDs or JAK inhibitors approved during the study are not permitted throughout the study treatment and until 4 weeks following the End-of-Treatment visit. If any of these treatments are used, the patient should be discontinued but the patient will continue to be followed up for safety for at least 4 additional weeks.

The use of **intramuscular (IM), IV and more than one intra-articular glucocorticoid injection** is not permitted throughout the study treatment and until 4 weeks following the End-of-Treatment visit. In cases where IM, IV, or more than intra-articular corticosteroids are needed, patient's withdrawal should be considered.

Immunization with a **live or attenuated vaccine** is prohibited within 4 weeks prior to Baseline, for the duration of study participation and 12 weeks after administration of the last dose of IMP.

Treatment with **any investigational medicinal product** other than sarilumab is not permitted.

8.8.2 Permitted medications

DMARDs: Treatment with csDMARDs (azathioprine, chloroquine, hydroxychloroquine, leflunomide, MTX, sulfasalazine), at a stable dose initiated at least 4 weeks prior to Baseline, is permitted during the study. If applicable, DMARDs can be used alone or in combination except for the combination of MTX and leflunomide. If applicable, patients should remain on the same background csDMARD(s) throughout the study.

The dose and route of administration of csDMARDs at entry in the study should be continued without change during the study period unless an adjustment is necessary for safety reasons. All biologic DMARDs are prohibited during the study and must be discontinued and washed out prior to the initiation of study treatment. The use of prohibited medications will require the patients to be withdrawn from the study.

Folic Acid: In order to minimize MTX toxicity, all patients treated with MTX will receive folic acid or equivalent at a dose of at least 5 mg/week. This can either be given as a single weekly dose usually 48 hours after MTX administration or be divided into daily doses to achieve at least 5 mg folic acid per week. It is the Investigator's decision as to which dosing regimen is used.

Oral corticosteroids: Patients may receive oral corticosteroids at dose of ≤15 mg/day prednisone or equivalent during the study, if initiated at least 4 weeks prior to Baseline. To treat AE for a condition not related to RA that requires a corticosteroid dose modification, increased doses of oral corticosteroids during the study will be permitted.

Corticosteroids can be stepwise discontinued at the investigator's discretion in eligible patients in order to achieve a steroid-free condition. After a potential increased dose of oral corticosteroids, up to 15 mg of prednisone daily (or equivalent), the corticosteroid dose should be tapered down to the previous level as rapidly as medically possible. In cases where increased corticosteroids doses for RA conditions can't be tapered down during the study, patient maintenance in the study should be reevaluated based on the investigator's judgment.

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

NSAIDs: Patients may be treated with NSAIDs or cyclo-oxygenase-2 inhibitors (COX-2) at a stable dose that was initiated at least 4 weeks prior to Baseline, up to the maximum recommended dose during the study. The dose should remain stable during the study, unless dose reduction is required for safety reasons. The choice and doses of NSAIDs and COX-2are at the discretion of the Investigator. The addition of new NSAIDs during the study treatment period is not permitted.

Analgesics (other than NSAIDs) and opioids: Analgesics and opioids up to the maximum recommended doses may be used for pain as required. However, patients should not take analgesics or opioids within 12 hours prior to a visit where clinical efficacy assessments are performed.

Lipid-lowering agents: Lipid lowering drugs are permitted. Dose should be stable for at least 6 weeks prior to screening. Anti-IL-6 drugs, including sarilumab, are known to increase serum

cholesterol levels and this effect will be closely monitored during the study. Use of lipid-lowering agents in patients with elevated lipids at any time during the study are strongly encouraged in conjunction with the treating physician's clinical judgment and guidelines such as National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III, see Appendix C).

8.8.3 Drug interactions

In vitro studies demonstrate that IL-6 reduces cytochrome CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzyme expression. Caution should be exercised in patients who will start sarilumab treatment while on therapy with CYP3A substrates (e.g. oral contraceptives or statins).

Sarilumab or tocilizumab, which antagonize IL-6, may normalize the formation of CYP450 enzymes. As a result, the therapeutic effect of drugs that are metabolized by these CYP450 isoforms may decrease when RA patients start receiving sarilumab. CYP450 substrates with a narrow therapeutic index should be monitored in patients that enter the treatment period. Some examples of CYP450 substrates with a narrow therapeutic index that require therapeutic monitoring (pharmacodynamics and/or drug concentration) include: warfarin, cyclosporine, theophylline, digoxin, antiepileptics like carbamazepine (Carbatrol®, Tegretol®), divalproex (Depakote®), phenytoin (Dilantin®), or valproic acid (Depakene®); or antiarrhythmics, like disopyramide (Norpace®), procainamide (Procan®, Pronestyl®), or quinidine (Quinidex®, Quin-Release Quin-G®).

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

- Change in the total RAID score from baseline to Week24.

The Rheumatoid Arthritis Impact of Disease (RAID) is a patient-reported outcome measure evaluating the impact of RA on patient quality of life which comprises 7 domains: pain, function, fatigue, physical and psychological wellbeing, sleep disturbance and coping.

Each domain is evaluated using a single question answered by a 0 to 10 numerical rating scale. Each domain also has a specific weight assigned by a patient survey. The RAID score is a continuous variable ranging from 0 (best) to 10 (worst) (see Appendix B).

The RAID score will be assessed at each assessment visit over the treatment period, from V2 (at first IMP administration) to V5 (at Week 24).

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoints (6-month core period)

9.2.1.1 Values at each assessment visit and changes from baseline for the total RAID score, HADS, MAThys, FACIT-Fatigue, HAQ-DI, morning stiffness, International Physical Activity Questionnaire, and patient global assessment of disease activity

All the studied PROs will be assessed at each visit over the treatment period (from V2 to V5). Questionnaires used are all valid and self-rating reliable scales.

The **Hospital Anxiety and Depression Scale (HADS)** measures anxiety and depression in both hospital and community settings. This questionnaire comprises 14 items divided into two subscales: anxiety and depression (see Appendix B). Each item is answered by a 0 to 3 rating scale, leading to maximum scores of 21 points for anxiety and depression. A total score up to 19 indicates a major depressive episode; a total score up to 13 indicates adjustment disorders and minor depression.

The **Multidimensional Assessment of Thymic States (MAThys)** is a multi-dimensional assisted self-administered questionnaire comprising five dimensions (emotional reactivity, cognition speed, psychomotor function, motivation and sensory perception) divided into 20 items relating to individual states as perceived by patients for the preceding week (see Appendix B). Each item is set out as a continuous measure in the form of a visual analogic scale of 10 cm on which the subject is asked to make a mark to indicate where he/she is positioned between the two predefined extreme propositions.

The **Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)** is a symptom-specific scale that measures fatigue in patients assess with chronic illness therapy over the 7 preceding days. This scale comprises 13 items scored on a 5-point Likert scale, from 0 (not at all) to 4 (very much) (see Appendix B). The figures are reversed during score calculations, so that higher score values indicate more favorable conditions. Total scores then range from 0 to 52, with lower scores representing greater fatigue.

The **Stanford Health Assessment Questionnaire Disability Index (HAQ-DI)** is a patient-oriented outcome assessment questionnaire specifically developed to assess the extent of a RA patient's functional ability. It consists of 20 questions referring to eight component sets: dressing/ grooming, arising, eating, walking, hygiene, reach, grip, and activities (see Appendix B). Knowing that here are 2 or 3 questions for each section, scoring within each section is from 0 (without any difficulty) to 3 (unable to do). The eight category scores are averaged into an overall HAQ-DI score on a scale from zero (no disability) to three (completely disabled). It is not truly continuous but has 25 possible values.

The **duration of morning stiffness** (in minutes) will be self-reported by RA patients.

The **International Physical Activity Questionnaire (IPAQ)** is a 27-item self-reported questionnaire designed to measure physical activity of patient. It comprises several parts (job-related, transport-related, domestic and leisure-time physical activity) and intensities (moderate, vigorous, walking) and includes sitting time (see Appendix B). Based on frequency, duration and intensity of self-reported physical activity, individuals are categorized into low, moderate and high physical activity groups.

The **patient global assessment of disease activity** measures RA activity as perceived by the patient, using a 100 mm horizontal visual analog scale (VAS).

9.2.1.2 Values at each assessment visit and changes from baseline for ESR, DAS28-ESR, CDAI, and joint counts (TJC, SJC)

At each visit, all the efficacy parameters will be assessed.

The **erythrocyte sedimentation rate (ESR)** is measured in mm/hr. This laboratory test will be performed in a local medical laboratory.

The DAS28 is a combined index for measuring disease activity in RA. The index includes the assessment of 28 joints for swelling and tenderness, acute phase response (ESR or CRP), and general health status. For this study, ESR will be used to calculate the DAS28 score. The index is calculated using the following formula:

DAS28-ESR = $0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \ln(ESR) + 0.014 \times PtGA$

where **TJC28** is the tender joint count on 28 joints, **SJC28** is the swollen joint count on 28 joints, ln is the natural log, ESR is the erythrocyte sedimentation rate (mm/hour), i.e., patient's global assessment of disease activity (PtGA using a 100 mm VAS). The 28 joints to be assessed are detailed in Appendix B.

The DAS28 scale ranges from 0 to 10, where higher scores represent higher disease activity.

The **CDAI** is a combined index for measuring disease activity in RA that does not include a laboratory test. It is calculated as follows:

CDAI = TJC28 + SJC28 + PtGA (in cm) + PhGA (in cm)

where TJC28 is the tender joint count on 28 joints, SJC28 is the swollen joint count on 28 joints, PtGA is patient's global assessment of disease activity (100mm VAS), and PhGA is the physician's global assessment of disease activity (100mm VAS). The 28 joints to be assessed are detailed in Appendix B.

9.2.1.3DAS28-ESR Low Disease Activity (LDA) and remission, CDAI LDA and remission, at W12 and W24

A DAS28-ESR score of <2.6 represents clinical remission and a score of ≤3.2 represents low disease activity.

A CDAI score of ≤2.8 represents clinical remission and a score of ≤10.0 represents low disease activity.

For both indexes, clinical remission is included in low disease activity.

9.2.2 Safety endpoints (6-month core and LTE periods)

Safety will be assessed, according to the Schedule of Assessment (see Section 1.2), based on reporting of adverse events (AEs), clinical laboratory results, physical examination, and vital signs.

9.2.2.1Adverse events

All AES, including serious AEs (SAEs) and AEs of special interest (AESIs) will be collected at every visit. Refer to Section 10.4 to Section 10.7 for details.

9.2.2.2Laboratory safety variables

The clinical laboratory data consist of blood analysis (including hematology, serum 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 analyses will be performed locally, according to the Schedule of Assessment (see Section 1.2):

- Hematology: hemoglobin, platelet count, and complete blood count (CBC)
- Serum chemistry and liver profile: creatinine clearance, serum iron and 25OHD (at Screening and Week 24 only), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin

- Serum lipids: total fasting cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol
- Serology: HbsAg, hepatitis B antibody, and hepatitis C virus antibody (at Screening only unless clinically indicated during the trial)
- Pregnancy test: Local pregnancy tests will be conducted for female patients of child-bearing potential. Pregnancy test at Screening will be a serum test. All following pregnancy tests will be urine tests. If a urine test is positive it must be confirmed by a serum pregnancy test
- TB test at Screening (or within the prior 90 days with no abnormality) unless clinically indicated during the trial.

Overnight fasting (>8 hours) prior to blood sampling is required for fasting samples. Patients will only be allowed to drink water during this time. Unscheduled laboratory assessments for safety issues are permitted at any time.

9.2.2.3 Vital signs

Vital signs include pulse rate, systolic and diastolic blood pressure, body weight, and waist circumference, according to the Schedule of Assessment (see Section 1.2). The blood pressures should be taken after the patient has been seated for at least 5 minutes.

9.2.2.4 Electrocardiogram variables

A standard 12-lead electrocardiogram (ECG) will be performed at the Screening visit.

9.2.2.5 Other safety endpoints

Not applicable.

9.3 OTHER ENDPOINTS

Not applicable.

9.4 FUTURE USE OF SAMPLES

Not applicable.

9.5 APPROPRIATENESS OF MEASUREMENTS

The assessments used in this study are standard for the evaluation of therapy in RA patients.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The visit schedule consists of the following visits:

- Screening Visit (V1). This visit will be performed over a 28-day period prior to Visit 2. No IMP will be administered during this period
- 6-month core period (D1 to Week 24). Four visits are planned after screening: V2 (baseline, first sarilumab injection at D1), V3 (Week 4 ± 3 days), V4 (Week 12 ± 7 days), and V5 (Week 24 ± 7 days)
- LTE period for patients who will complete the 6-month core period: V LTE1 (Week 36 ± 7 days) and V LTE2 (Week 48 ± 7 days) or until the commercial availability of sarilumab in France
- Post-treatment observations (V6). One visit is planned between two and four weeks after the last IMP administration.

In case of premature withdrawal, the patient should perform a specific visit as soon as possible after the last IMP dose administration.

The visits' schedule is detailed in section 1.2. If a visit date is changed, the next visit should take place according to the original schedule.

The patients will be requested to complete PROs questionnaires during their clinical visits (at each visit over the 6-month core period and at premature withdrawal if applicable), before any other assessments. Over the treatment period, when IMP administration is performed at the time of an assessment visit, the injection should be done after all study assessments.

10.1.1 Screening (Visit 1: Day -28 to Day -1)

Written informed consent for participation in the study must be obtained before performing any study-specific Screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations will be performed within 28 days prior to Baseline (see details in Section 1.2). Patients must fulfill all entry criteria specified in Section 7 and provide background clinical information in order to participate in the study. If a patient fails any inclusion/exclusion criteria at Screening, the patient may be re-screened depending on the inclusion/exclusion criteria he/she failed and upon authorization by the Sponsor.

An Eligibility Screening Form documenting the Investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator. A screen failure log must be maintained by the Investigator.

The following items will be checked and recorded by the Investigator or designee:

- Assess eligibility by review of inclusion/exclusion criteria. Patients who do not meet these inclusion/exclusion criteria should not continue the screening process.
- Record patient's demography, previous medical and surgical history. Medical history should include RA history to confirm the diagnosis and TB history in particular.
- A general physical examination should be performed during the Screening period (between D-28 and D-1).
- Record the size of the largest rheumatoid nodule (if applicable), considering that the effect of DMARD on rheumatoid nodules are still being debated
- If at Baseline a chest X-ray has been performed within 90 days that shows no clinically significant abnormality, a further chest X-ray is not required. A 12-lead ECG should be performed during the Screening period.
- Record vital signs [pulse rate, systolic and diastolic blood pressure (while seated)].
- If a tuberculosis assessment (QUANTIFERON, performed locally) has been performed within 90 days that shows no abnormality, a further tuberculosis assessment is not required over the Screening period and at the following study visits, unless clinically indicated during the trial.
- Obtain blood sample serum for female patients of child-bearing potential for β-HCG pregnancy test
- Obtain fasting blood samples during the Screening period (performed locally) including hematology [hemoglobin, complete blood count (CBC), platelet count, and erythrocyte sedimentation rate (ESR)], serum chemistry [creatinine clearance, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin count], serum iron, 25OHD, fasting lipids [total fasting cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol], and serology (hepatitis B surface antigen, hepatitis B antibody, and hepatitis C antibody) during the Screening period only unless clinically indicated during the trial). *Hematology, serum chemistry, and fasting lipid tests have to be performed over the 7-day period before inclusion.*
- Any clinically significant abnormalities should be recorded and documented in medical/surgical history
- Complete the ACR core set assessments including ESR, DAS28-ESR, CDAI, and joint counts (TJC and SJC on 28 joints).
- Patients who meet all the inclusion criteria and none of the exclusion criteria will be eligible for the baseline visit.

10.1.2 Baseline examination (Visit 2: first IMP administration)

All Baseline investigations will be performed according to the Schedule of Assessments (see details in Section 1.2).

All PROs and efficacy assessments performed at the Baseline visit should occur the same day and before the first administration of sarilumab.

The investigator or designee will:

- Assess eligibility by review of inclusion/exclusion criteria. Patients who do not meet these inclusion/exclusion criteria should be excluded from the study prior any study treatment administration.
- Record the general physical examination performed during the Screening period (between D-28 and D-1), and reported V2 body weight and waist circumference.
- Record Baseline chest X-ray and 12-lead ECG.
- Record vital signs.
- Ask the patient to complete the following self-assessments: RAID, HADS, MAThyS, FACIT-Fatigue, HAQ-DI, duration of morning stiffness, IPAQ, and patient global assessment of disease activity (VAS)
- For female patients of child-bearing potential performed a urine pregnancy test. If the urine test is positive it must be confirmed by a serum pregnancy test.
- Record the results of hematology, serum chemistry, serum iron, 25OHD, fasting lipids, and serology tests results
- Complete the ACR core set assessments including ESR, DAS28-ESR, CDAI, and joint counts (TJC and SJC on 28 joints).
- Review concomitant medications
- Inquire about and record any adverse events/SAEs that could have occurred since the signature of the written consent form.
- If the patient meet all the inclusion criteria and none of the exclusion criteria, proceed to the first SC administration of the IMP
- For patients able to perform SC injections at home, the investigator or delegate will provide training regarding the preparation and injections (at Baseline). For patients and/or non-professional caregivers completely unable to perform such injections at home, a home nursing will be needed and arrangements must be made to administer IMP at 2-week intervals.
- Deliver IMP for the next study period.
- Schedule an appointment for the next visit.

For all subsequent visits, the scheduled day should be followed (see details in Section 1.2).

10.1.3 Assessments during the 6-month core period (Visit 3 to Visit 5)

All assessments must be performed on the day of the specified visit (see details in Section 1.2). For local laboratory tests required at a given visit (results should be available at this study time-point), a time window of 3 days prior the visit is allowed.

The investigator or designee will:

- Body weight and waist circumference have to be reported only at V5.
- Record vital signs.
- Record the size of the largest rheumatoid nodule (if applicable), only at V5.
- Ask the patient to complete the following self-assessments: RAID, HADS, MAThyS, FACIT-Fatigue, HAQ-DI, duration of morning stiffness, IPAQ, and patient global assessment of disease activity (VAS)
- For female patients of child-bearing potential performed a urine pregnancy test. If the urine test is positive it must be confirmed by a serum pregnancy test.
- Record the results of hematology, serum chemistry, and fasting lipids results at each visit; serum iron and 25OHD at the V5 visit only
- Complete the ACR core set assessments including: ESR, DAS28-ESR, CDAI, and joint counts (TJC and SJC on 28 joints).
- Review concomitant medications
- Assess IMP compliance / review patient diary
- Inquire about and record any adverse events/SAEs.
- Deliver IMP for the next study period
- Schedule an appointment for the next visit.

10.1.4 .Assessments during the LTE period (Visit LTE1 and Visit LTE2)

All the patients who will complete the 6-month-core period are allowed to enter the LTE period in order to continue the treatment with sarilumab (as monotherapy or in combination) for a maximum of another 24 weeks or until the commercial availability of sarilumab in France

All assessments must be performed on the day of the specified visit (see details in Section 1.2). For local laboratory tests required at a given visit (results should be available at this study time-point), a time window of 3 days prior the visit is allowed.

The investigator or designee will:

- Record vital signs.
- For female patients of child-bearing potential performed a urine pregnancy test. If the urine test is positive it must be confirmed by a serum pregnancy test.
- Record the results of hematology, serum chemistry, and fasting lipids results
- Review concomitant medications
- Assess IMP compliance / review patient diary
- Inquire about and record any adverse events/SAEs.

- Deliver IMP for the next study period
- Schedule an appointment for the next visit.

10.1.5 Assessments at early termination visit

If a patient withdraws from the study at any time point, an early withdrawal visit must be completed as soon as possible after the last dose of study drug. If a patient withdraws at a visit, this visit should proceed as an early withdrawal visit. In this case, only the withdrawal visit assessments should be conducted.

The investigator or designee will:

- Record body weight and waist circumference.
- A general physical examination should be performed.
- Record vital signs.
- Record the size of the largest rheumatoid nodule (if applicable).
- Ask the patient to complete the following self-assessments: RAID, HADS, MAThyS, FACIT-Fatigue, HAQ-DI, duration of morning stiffness, IPAQ, and patient global assessment of disease activity (VAS)
- For female patients of child-bearing potential performed a urine pregnancy test. If the urine test is positive it must be confirmed by a serum pregnancy test.
- Record the results of hematology, serum chemistry, serum iron, 25OHD, and fasting lipids results.
- Complete the ACR core set assessments including: ESR, DAS28-ESR, CDAI, and joint counts (TJC and SJC on 28 joints).
- Review concomitant medications
- Assess IMP compliance / review patient diary
- Inquire about and record any adverse events/SAEs.
- Record the reason(s) for early termination.

10.1.6 Post-treatment observations (Visit PT)

Between 2 and 4 weeks after the last IMP administration (Visit PT), the patient will be required to perform a follow-up visit as detailed in Section 1.2.

The investigator or designee will:

- Record vital signs.
- For female patients of child-bearing potential performed a urine pregnancy test. If the urine test is positive it must be confirmed by a serum pregnancy test.
- Review concomitant medications.

- Assess IMP compliance / review patient diary
- Inquire about and record any adverse events/SAEs.

10.2 DEFINITION OF SOURCE DATA

Source documents are defined as original documents, data, and records. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, photographic negatives, microfilm or magnetic media, X-rays and ECG tracings, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

For this study, source documents notably include:

- PROs assessments completed par patients (RAID, HADS, MAThyS, FACIT-Fatigue, HAQ-DI, duration of morning stiffness, IPAQ, and patient global assessment of disease activity)
- Physician global assessment of disease activity
- TJC and SJC
- Patient Home Dosing Diaries.

10.3 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.

10.3.1 Temporary treatment discontinuation with investigational medicinal product

Temporary treatment discontinuation decided by the Investigator corresponds to more than one sarilumab injection not administered to the patient. A temporary treatment discontinuation greater than 31 days has to be considered as permanent.

Temporary treatment discontinuation may be considered by the Investigator because of suspected or confirmed AEs. Re-initiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to the Section 7).

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

10.3.2 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 at any time during the study, or from the patient not to be re-exposed to the IMP whatever the reason.

10.3.3 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.

Patients must discontinue sarilumab if they experience any of the following:

- Pregnancy in female patients
- Opportunistic infections (including but not limited to tuberculosis and disseminated herpes zoster) and serious infections
- Gastro-intestinal perforations or diverticulitis
- Neutropenia (ANC <500 cells/mm^3)
- Thrombocytopenia (platelet count <50,000 cells/mm^3)
- ALT or AST elevation of >5 times ULN
- Malignancies (with the exception of local basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that have been excised and cured)
- Signs/symptoms of anaphylaxis or hypersensitivity following SC administration of sarilumab
- Use of biologic DMARD other than sarilumab
- Any AEs, per Investigator's judgment, that may jeopardize the patient's safety.

Any abnormal laboratory value will be immediately rechecked for confirmation before deciding of permanent discontinuation of IMP treatment.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures 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.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the IMP (see Section 1.2).

All cases of permanent treatment discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

10.3.5 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 without any effect on their care. However, if patients no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Patients who withdraw from the study treatment should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

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

In addition, a patient may withdraw his/her consent to stop participating in the study. Withdrawal of consent for 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 record checks. The site should document any case of withdrawal of consent.

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator must 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 retreated in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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

10.4.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

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

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc.).
- Development of drug dependence or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality

- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study
- Suspected transmission of an infectious agent.

10.4.1.3 Adverse event of special interest

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

Any AESIs will be reported to the Sponsor in the same timeframe as SAEs, ie, within 24 hours, as detailed in Section 10.4.5.

For this study, AESIs are defined as:

- Pregnancy of a female subject in the study
  - It will be qualified as a SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2)
  - In the event of pregnancy in a female participant, IMP should be discontinued
  - Follow-up of the pregnancy in a female participant is mandatory until the outcome has been determined (see Appendix A).
- Symptomatic overdose (serious or non-serious) with IMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least twice the dose during the planned intervals.

  Of note, asymptomatic overdose has to be reported as a standard AE.

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

Not applicable.

10.4.3 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.
- 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.

Instructions for AE reporting are summarized in Table 1.

10.4.4 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.

10.4.5 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.4, even if not fulfilling a seriousness criterion, using the corresponding screens in the eCRF.

Instructions for AE reporting are summarized in Table 1.

10.4.6 Guidelines for management of specific laboratory abnormalities

Recommended dose modifications in case of neutropenia, thrombocytopenia, or liver enzyme elevations are provided in the following tables.

Low Absolute Neutrophil Count	
Lab Value (cells x 10^9/L)	**Recommendation**
ANC greater than 1	Current dose of sarilumab should be maintained.
ANC 0.5-1	Treatment with sarilumab should be withheld until >1 x 10^9/L. Sarilumab can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
ANC less than 0.5	Discontinue sarilumab.

Low Platelet Count	
Lab Value (cells x 10^3/µL)	**Recommendation**
50 to 100	Treatment with sarilumab should be withheld until >100 x 10^3/µL. Sarilumab can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
Less than 50	If confirmed by repeat testing, discontinue sarilumab.

Liver Enzyme Abnormalities	
Lab Value	**Recommendation**
ALT >1 to ≤ 3 x ULN	Consider dose modification of concomitant DMARDs as clinically appropriate.

Liver Enzyme Abnormalities	
Lab Value	**Recommendation**
ALT >3 x and ≤5 x ULN	Treatment with sarilumab should be withheld until < 3 x ULN. Sarilumab can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
ALT >5 x ULN	Treatment with sarilumab should be discontinued.

10.4.7 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.

Table 1 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No

10.5 OBLIGATIONS OF THE SPONSOR

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

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, independent ethics committee (IRB/IEC) 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.

- The AESIs (listed in section 10.4.5) to those regulatory authorities who require such reporting.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected. RA flares are not considered as AEs. Any other AE not listed as an expected event in the summary of product characteristics or in this protocol will be considered unexpected.

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

10.6 SAFETY INSTRUCTIONS

Please refer to serious adverse events reporting (see Section 10.4.4), adverse event of special interest (see Section 10.4.5) definitions and reporting, and guidelines for management of specific laboratory abnormalities (Section 10.4.6).

Infections

Biologics including sarilumab have been associated with an increased risk of infections. Physicians should then exercise caution when considering the use of sarilumab in patients with a history of recurring infections or with underlying conditions (e.g., diabetes mellitus) which may predispose patients to infections. Sarilumab should not be administered in patients with active infection. Therefore patients with active current infection or a history of recurring infection (including but not limited to active TB or history of incompletely treated TB and atypical mycobacterial disease, hepatitis B and C, and herpes zoster) will be excluded from the study.

The effects of sarilumab on acute reactants, neutrophils, and the signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Any infection should be reported by the Investigator as an adverse event and a corresponding eCRF form should be filled in (type of infection, treatment with antibiotics if any with route of administration).

As all biologics, sarilumab may induce immunosuppression, increasing the risk of reactivation of latent TB. As a precautionary measure, patients with active 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, notably based on physical examination, negative chest X-ray and TB test over the Screening period.

NOTE: in case of latent TB infection the patient may be included if a subsequent appropriate anti TB treatment is initiated since at least 3 weeks

Systemic hypersensitivity reactions/anaphylaxis

As infrequent, mild-moderate, systemic hypersensitivity reactions have been observed with sarilumab, the patient should be monitored for 30 minutes after the IMP injection when given at the study site. Also patient should be advised, when IMP is administered at home, to self-monitor for potential signs and symptoms that may suggest a hypersensitive reaction for 30 minutes after administration. Any problems should be documented in the patient's Home Dosing Diary or in the medical notes and reported as AE. In case of systemic hypersensitivity reaction, the IMP should be discontinued and those events meeting seriousness criteria (e.g., hospitalization, life threatening, etc.; see Section 10.4.1.2) should be reported as SAEs.

Signs of a possible hypersensitivity reaction include but are not limited to:

- Fever, chills, pruritus, urticaria, angioedema, and skin rash.
- Cardiopulmonary reactions, including chest pain, dyspnea, hypotension, or hypertension.

If clinical criteria for anaphylaxis are met, appropriate treatment should be administered immediately and the event should be reported as a SAE.

Diverticulitis and gastrointestinal perforation

Symptomatic diverticulosis, diverticulitis, or chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis, or other chronic lower GI conditions might predispose to perforations. Therefore patients with a history of previous gastrointestinal perforation or diverticulitis will be excluded from the study.

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 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 is an AESI with immediate notification to be reported as SAE (see Section 10.4.4). Confirmed diverticulitis or gastrointestinal ulceration should be reported as AEs.

Management of dyslipidemia

Patients treated with sarilumab have been observed to have increased elevations of all lipid parameters, and RA is a known independent risk factor for cardiovascular events. Therefore, as a precautionary measure, patients with severe uncontrolled fasting hypercholesterolemia (>3.5 g/L [9.1 mmol/L]) or hypertriglyceridemia (>5.00 g/L [5.6 mmol/L]) will be excluded from the study.

Patients who are found to have dyslipidemia during the course of the study should be treated according to the National Cholesterol Education Program (NCEP)/Adult Treatment Panel 3 (ATP3; See Appendix C) or applicable local guideline. Also see Section 8.8.2 under concomitant medication rules for lipid-lowering therapy.

Local injection site reactions

In previous clinical trials, no clinically significant injection site reactions (ISRs) were observed. Local ISRs, including but not limited, to erythema, induration, pain, and SC emphysema, should be reported as an AE, with the event term recorded in AE eCRF as the symptom followed by 'at injection site' (i.e. 'erythema at injection site'). If needed, ISRs should be treated topically and the treatment(s) should be reported in the eCRF.

10.7 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 primary study objective is to assess the change in RAID score from baseline to W24. A sufficient precision (half-length of the 95% confidence interval) is required. According to the literature (44, 45, 46) and findings from the MONARCH and TARGET studies (22, 33), the standard deviation (SD) of the RAID score could be estimated at 2.5 points. On this basis, a sample size of 140 patients (122 evaluable, if 20% non-evaluable patients) produces a precision, two-sided 95% confidence interval (CI), with a distance from the mean to the limits that will be less than 0.5 when the estimated SD is 2.5. Table below gives the 95% CI of change from baseline to W24 of RAID score with this precision (0.44), assuming that the change from baseline will be from 30% to 50% (MCII defined by Dougados in 2012; 47) of baseline score.

Expected change from baseline to W24 of RAID score (Relative to baseline %)	RAID score at Baseline	Expected change from baseline to W24 of RAID score (Absolute value)	95% CI (precision =0.5)
30%	65	2,0	[1,5 ; 2,5]
	5	1,5	[1,0 ; 2,0]
	3,5	1,1	[0,6 ; 1,6]
50%	**6,5**	**3,3**	**[2,8; 3,8]**
	5	2,5	[2,0 ; 3,0]
	3,5	1,8	[1,3 ; 2,3]

Note that on MONARCH study (22), the % of change from baseline was 49.6% (3.32/6/69) and in TARGET study (33) 47.4% (3.24/6.83).

11.2 DISPOSITION OF PATIENTS

Disposition of patients will be depicted for patient status and patient analysis populations. The total number of patients for each of the following categories will be described:

- Enrolled patients
- Patients failed to be enrolled and the reason for non-enrollment
- Safety population
- ITT population
- Per-Protocol population.

11.3 ANALYSIS POPULATIONS

11.3.1 Intent-to-treat population

Intent-to-treat (ITT) population: all patients who met all the eligibility criteria and who are actually treated.

11.3.2 Safety population

Safety population: all patients who have signed the Informed Consent Form (ICF) and have been exposed to at least one dose or part of a dose of IMP.

11.3.3 Per-protocol population

Per-protocol population: patients of ITT population without major protocol deviations. Major deviations will be defined in the statistical analyses plan before database frozen.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

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

11.4.1.1 Extent of investigational medicinal product exposure

The duration of IMP exposure is defined as follows last dose date – first dose date + 14 days regardless of unplanned intermittent discontinuations.

The IMP dose as well as temporary and permanent discontinuations of the IMP will be described (with reasons).

11.4.1.2 Demographic and baseline characteristics

All demographic and baseline characteristics will be summarized in the ITT population using descriptive statistics.

11.4.1.3 Compliance

A given administration will be considered non-compliant if the patient did not take the planned dose of treatment 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 <80% will be summarized.

11.4.1.4 Prior and concomitant treatments

The prior and concomitant medications will be presented for the Safety population.
Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the ATC class (anatomic category) and the first three digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized. Patients will be counted once in each ATC categories (anatomic or therapeutic) linked to the medication, therefore patients may be counted several time for the same medication.
The table for prior and concomitant medications will be sorted by decreasing frequency of anatomic category followed by all other therapeutic classes. In case of equal frequency regarding anatomic categories, alphabetical order will be used.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint

The primary study objective is to assess the change in RAID score from baseline to W24. The number of available data, mean, standard deviation, median and range (minimum, maximum) will be provided with the 95% confidence interval of mean change from baseline to W24.
Main analysis will be done on ITT population. Sensitivity analysis will be conducted in reproducing the same analysis using the per-protocol population.

In addition, multivariate analyses such as ANCOVA (Analyze of Covariance), Logistic Regression and Multiple Correspondences analysis can be performed from baseline in order to exploratory explain different profiles of patients. The details of theses analyses will be described on the statistical analyses plan before database frozen.

In case of any event mentioned below, the last available endpoint before the considered event will be taken in account (for RAID score for primary endpoint and for all other secondary endpoints):

- Lack of efficacy
    - More than one glucocorticoid infiltration per articulation
    - Dose increase of an ongoing glucocorticoid or start of systemic glucocorticoid treatment
    - Change in NSAID due to lack of efficacy or adverse event considered as related to treatment by the investigator
- Missing data
    - Treatment discontinuation due to lack of efficacy or adverse event (except for AEs due to NSAID). For all other cases, missing data will not be replaced.

11.4.2.2 Secondary analyses

All secondary parameters will be described. For continuous variables, the number of available data, mean, standard deviation, median and range (minimum, maximum) will be provided. Categorical variables will be summarized using number and percentage of patients. Patients with missing data will not be included in the calculation of percentages. 95% CI will be provided.

11.4.2.3 Multiplicity considerations

Not applicable: all analyses are descriptive without test.

11.4.3 Analyses of safety data

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

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

- 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. These abnormal values will be detailed in the Statistical Analysis Plan that will be validated before the database freezing.
- 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.

Death. The following deaths summaries will be generated:

- Number (%) of patients who died by study period (treatment-emergent AEs, on-study) and reasons for death summarized on the safety population
- All AEs leading to death (death as an outcome on the AE CRF/eCRF 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
- TEAE leading to death (death as an outcome on the AE CRF/eCRF 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.

11.5 INTERIM ANALYSIS

Not applicable

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 consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

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

12.2 INFORMED CONSENT

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

Prior to a patient’s participation in the clinical trial, the written ICF should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF will be provided to the patient.

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

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

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

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed [clinical trial protocol, ICF, labeling documents (summary of product characteristics, package insert), Investigator’s curriculum vitae, 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 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 e-CRF, 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 Sub-investigator 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 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, 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 Subinvestigators 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.

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 Sub-investigator, 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.

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17 APPENDICES

Appendix A Contraceptive guidance and collection of pregnancy information

DEFINITIONS

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) 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 measurement is insufficient.
   - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal 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 enrollment.

CONTRACEPTION GUIDANCE

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the following Table.

Table 2: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral

– intravaginal – transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation – oral – injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] - Intrauterine device (IUD) - Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be utilized during the treatment period and for up to 3 months after treatment after the last dose of study treatment.

Appendix B Document(s) related to the assessment of 1 (or more) endpoint(s)

2010 ACR-EULAR Classification Criteria for Rheumatoid Arthritis

Target population (who should be tested?)
Patient with at least 1 swollen joint with definite clinical synovitis (swelling).* Synovitis is not better explained by another disease. *Differential diagnoses differ in patients with different presentations but may include conditions such as systemic lupus erythematosus, psoriatic arthritis and gout. If unclear about the relevant differentials, an expert rheumatologist should be consulted.

Classification criteria for RA (Score-based algorithm: add score of categories A-D) A score of ≥ 6/10 is needed for a definite classification of a patient with RA.	
Joint involvement[A]	
1 large[B] joint	0
2-10 large joints	1
1-3 small[C] joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints[D] (at least one small joint)	5
Serology[E] (at least one test result is needed for classification)	
Negative RF **and** negative ACPA	0
Low positive RF **or** low positive ACPA	2
High positive RF **or** high positive ACPA	3
ACUTE PHASE REACTANTS[F] (at least one test result is needed for classification)	
Normal CRP **and** normal ESR	0
Abnormal CRP **or** abnormal ESR	1
Duration of symptoms[G]	
< 6 weeks	0
≥ 6 weeks	1

[A]Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints (DIPs), 1st carpo-metacarpal (CMC) joint, and 1st metatarso-phalangeal (MTP) joint are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of the involved joints, with placement into the highest category possible based on the pattern of joint involvement.

[B]Large joints refer to shoulders, elbows, hips, knees and ankles.

[C]Small joints refer to the wrists, metacarpo-phalangeal (MCP) joints, proximal interphalangeal (PIP) joints, thumb interphalangeal (IP) joints and metatarsophalangeal (MTP).

[D]In this category, at least 1 of the involved joints must be a small joint ; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g. temperomandibular, acromioclavicular and sternoclavicular joints).

[E]Negative refers to international unit (IU) values that are £ upper limit of normal ULN for the lab and assay. Low titre refers to IU values that are > ULN but £ 3X ULN for lab and assay. High titre positive: > 3X ULN for lab and assay. Where RF is only available as positive or negative, a positive results should be scored as 'low positive' for RF.

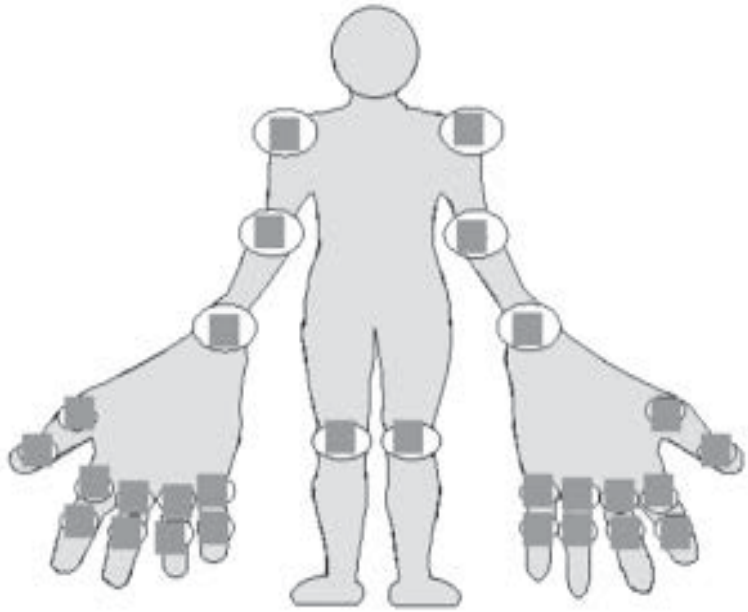
[F]Normal /abnormal is determined by local laboratory standards (*Other causes for elevated acute phase reactants should be excluded*).

[G]Duration of symptoms refers to patient self-report of the duration of signsor symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

RF = rheumatoid factor; ACPA = anti-citrullinated protein/ peptide antibodies; ULN = upper limit of normal; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

APPENDIX

The 28 joints to be assessed are as followed.



APPENDIX

RAID (Rheumatoid Arthritis Impact of Disease)

1. Pain

Circle the number that best describes the pain you felt due to your rheumatoid arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

2. Functional disability assessment

Circle the number that best describes the difficulty you had in doing daily physical activities due to your rheumatoid arthritis during the last week:

No difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme difficulty

3. Fatigue

Circle the number that best describes how much fatigue you felt due to your rheumatoid arthritis during the last week:

No fatigue	0	1	2	3	4	5	6	7	8	9	10	Totally exhausted

4. Sleep

Circle the number that best describes the difficulty the sleep difficulties (*i.e.*, resting at night) you felt due to your rheumatoid arthritis during the last week:

No difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme difficulty

5. Physical well-being

Considering your arthritis overall, how would you rate your level of physical wellbeing during the past week? Circle the number that best describe your level of physical well-being:

Very good	0	1	2	3	4	5	6	7	8	9	10	Very bad

6. Emotional well-being

Considering your arthritis overall, how would you rate your level of emotional well being during the past week? Circle the number that best describes your level of emotional well-being:

Very good	0	1	2	3	4	5	6	7	8	9	10	Very bad

7. Coping

Considering your arthritis overall, how well did you cope (manage, deal, make do) with your disease during the last week:

Very well	0	1	2	3	4	5	6	7	8	9	10	Very poorly

APPENDIX

HADS (Hospital Anxiety and Depression Scale)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

APPENDIX

FACIT-Fatigue (Functional Assessment of Chronic Illness Therapy – Fatigue) – Version 4

Below is a list of statements that other people with your illness have said are important. **Please cir**
or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

APPENDIX

HAQ-DI (Health Assessment Questionnaire – Disability Index)

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
DRESSING & GROOMING				
Are you able to:				
Dress yourself, including shoelaces and buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
Stand up from a straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
Cut your own meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Devices used for Dressing (button hook, zipper pull, etc.)
☐ Built up or special utensils
☐ Crutches
☐ Cane
☐ Wheelchair
☐ Special or built up chair
☐ Walker

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming
☐ Arising
☐ Eating
☐ Walking

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
HYGIENE				
Are you able to:				
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open previously opened jars?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat
☐ Bathtub bar
☐ Long-handled appliances for reach
☐ Bathtub seat
☐ Long-handled appliances in bathroom
☐ Jar opener (for jars previously opened)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene
☐ Reach
☐ Gripping and opening things
☐ Errands and chores

Your ACTIVITIES: To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

COMPLETELY	MOSTLY	MODERATELY	A LITTLE	NOT AT ALL
☐	☐	☐	☐	☐

Your PAIN: How much pain have you had IN THE PAST WEEK?
On a scale of 0 to 100 (where zero represents “no pain” and 100 represents “severe pain”), please record the number below.

Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (0 represents “very well” and 100 represents “very poor” health), please record the number below.

APPENDIX

IPAQ (International Physical Activity Questionnaire))

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

   ☐ Yes

   ☐ No → ***Skip to PART 2: TRANSPORTATION***

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

   _____ **days per week**

   ☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

   _____ **hours per day**
   _____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

   _____ **days per week**

   ☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**
_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**
_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**
_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**
_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**
_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**
_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**
_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?
_____ **hours per day**
_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**
_____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**
_____ **minutes per day**

This is the end of the questionnaire, thank you for participating.

APPENDIX

Auto-questionnaire MAThys

Consignes : Cette échelle a pour but d'évaluer votre état au cours de la **dernière semaine écoulée**. Pour chaque item, indiquez par un trait où vous pensez vous situer en fonction des deux propositions sachant que le centre du trait représente votre état habituel.

1- Je suis moins sensible que d'habitude aux couleurs.	———	Je suis plus sensible que d'habitude aux couleurs.
2- Je manque de tonus.	———	J'ai une tension musculaire importante.
3- J'ai l'impression d'être anesthésié(e) sur le plan des émotions.	———	J'ai parfois le sentiment de perdre le contrôle de mes émotions.
4- Je suis replié(e) sur moi.	———	Je suis désinhibé(e).
5- Je suis facilement distrait(e), la moindre chose me fait perdre mon attention.	———	Je ne suis pas attentif à mon environnement
6- Je suis plus sensible que d'habitude au toucher.	———	Je suis moins sensible que d'habitude au toucher.
7- J'ai l'impression que mon humeur varie beaucoup en fonction de mon environnement.	———	Mon humeur est monotone et peu changeante.
8- Je suis particulièrement sensible à la musique.	———	Je suis plus indifférent que d'habitude à la musique.
9- Mon cerveau ne s'arrête jamais.	———	Mon cerveau fonctionne au ralenti.
10- Je suis plus réactif(ve) à mon environnement.	———	Je suis moins réactif à mon environnement.

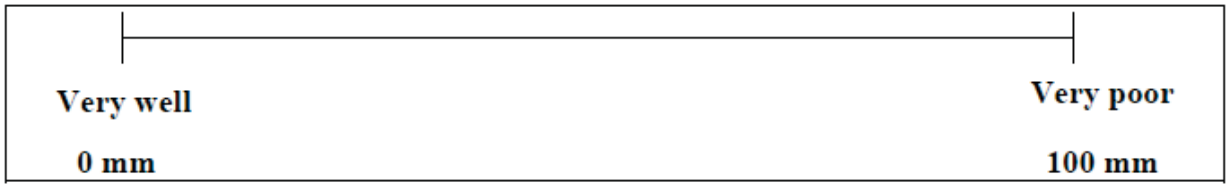
11- Je me sens sans énergie.	———	J'ai le sentiment d'avoir une grande énergie.
12- J'ai le sentiment que mes pensées sont ralenties.	———	J'ai le sentiment que mes idées défilent dans ma tête.
13- Je trouve la nourriture sans goût.	———	Je recherche les plaisirs gastronomiques car j'en apprécie davantage les saveurs.
14- J'ai moins envie de communiquer avec les autres.	———	J'ai plus envie de communiquer avec les autres.
15- Je manque de motivation pour aller de l'avant.	———	Je multiplie les projets nouveaux.
16- Ma perte d'intérêt pour mon environnement m'empêche de gérer le quotidien.	———	J'ai envie de faire plus de choses que d'habitude.
17- Je prends les décisions de manière plus rapide que d'habitude.	———	J'ai plus de difficultés que d'habitude à prendre des décisions.
18- Je ressens les émotions de manière très intense.	———	Mes émotions sont atténuées.
19- Je suis ralenti(e) dans mes mouvements.	———	Je suis physiquement agité(e).
20- J'ai l'impression d'être moins sensible aux odeurs que d'habitude.	———	J'ai l'impression d'être plus sensible aux odeurs que d'habitude.

SCORE |___|___|___| cm

APPENDIX

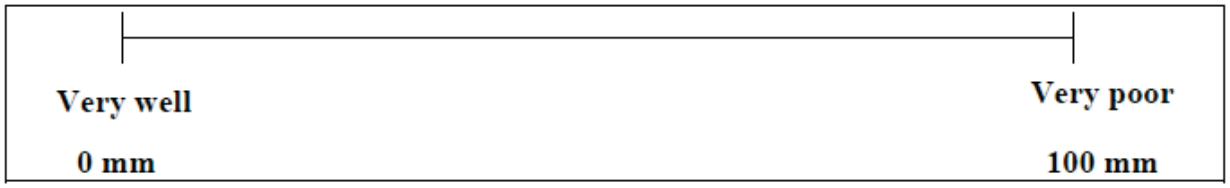
Patient global assessment of disease activity

Considering all the ways that your rheumatoid arthritis affects you, rate how you are doing on the following scale by placing a vertical mark on the line:



Physician global assessment of disease activity

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



Appendix C Other specific appendices for a given clinical trial

New York Heart Association Classification of Heart Failure

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea).
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of fatigue, rapid/irregular heartbeat (palpitation) or shortness of breath (dyspnea) are present at rest. If any physical activity is undertaken, discomfort increases.

APPENDIX

National Cholesterol Education Program Adult Treatment Panel III

National Cholesterol Education Program

ATP III Guidelines At-A-Glance Quick Desk Reference

1

Step 1

Determine lipoprotein levels–obtain complete lipoprotein profile after 9- to 12-hour fast.

ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol – Primary Target of Therapy	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

2

Step 2

Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):

- Clinical CHD
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm.

3

Step 3

Determine presence of major risk factors (other than LDL):

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals

Cigarette smoking
Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
Low HDL cholesterol (<40 mg/dL)*
Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
Age (men ≥45 years; women ≥55 years)

** HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.*

- Note: in ATP III, diabetes is regarded as a CHD risk equivalent.

APPENDIX
SmPC sarilumab