NCT01146652

AMENDED CLINICAL TRIAL PROTOCOL 9

COMPOUND: Sarilumab (SAR153191)

A multi-center, uncontrolled extension study evaluating the efficacy and safety of sarilumab in patients with active Rheumatoid Arthritis (RA)

STUDY NUMBER: LTS11210

STUDY NAME: SARIL-RA-EXTEND

VERSION DATE / STATUS: 31-Aug-2015 / Approved

CLINICAL STUDY DIRECTOR: [redacted]

Protocol Amendment 9	Version number: 1 (electronic 1.0)	Date: 31-Aug-2015
Amended Clinical Trial Protocol 8	Version number: 1 (electronic 10.0)	Date: 17-Jul-2014
Protocol Amendment 8 (includes local amendments 6 and 7)	Version number: 1 (electronic 2.0)	Date: 17-Jul-2014
Amended Clinical Trial Protocol 7 (Local-UK)	Version number: 1 (electronic 6.0)	Date: 01-Jul-2013
Protocol Amendment 7 (Local-UK)	Version number: 1 (electronic 1.0)	Date: 01-Jul-2013
Amended Clinical Trial Protocol 6 (Local-Portugal)	Version number: 1 (electronic 2.0)	Date: 27-Mar-2013
Protocol Amendment 6 (Local-Portugal)	Version number: 1 (electronic 1.0)	Date: 27-Mar-2013
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Protocol Amendment 5	Version number: 1 (electronic 1.0)	Date: 31-Oct-2012
Amended Clinical Trial Protocol 4	Version number: 1 (electronic 6.0)	Date: 08-Aug-2012
Protocol Amendment 4	Version number: 1 (electronic 1.0)	Date: 08-Aug-2012
Amended Clinical Trial Protocol 3	Version number: 1 (electronic 5.0)	Date: 24-Jan-2012
Protocol Amendment 3	Version number: 1 (electronic 1.0)	Date: 24-Jan-2012
Amended Clinical Trial Protocol 2	Version number: 3 (electronic 4.0)	Date: 26-May-2011
Protocol Amendment 2	Version number: 1 (electronic 2.0)	Date: 26-May-2011
Amended Clinical Trial Protocol 1	Version number: 2 (electronic 2.0)	Date: 10-Jan-2011
Protocol Amendment 1	Version number: 2 (electronic 2.0)	Date: 10-Jan-2011
Clinical Trial Protocol	Version number: 1 (electronic 3.0)	Date: 16-Feb-2010

EudraCT or IND number: 2010-019262-86 / 100,632

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	[redacted]
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	Sanofi recherche & développement 1 avenue Pierre Brossolette 91380 Chilly-Mazarin Cedex FRANCE
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: Sarilumab	**STUDY No.: LTS11210**
TITLE	A multi-center, uncontrolled extension study evaluating the efficacy and safety of sarilumab in patients with active Rheumatoid Arthritis (RA).
INVESTIGATOR/TRIAL LOCATION	Worldwide
STUDY OBJECTIVE(S)	To document the long term safety and efficacy of sarilumab.
STUDY DESIGN	An uncontrolled open label extension study of sarilumab 200 mg every other week (q2w); lasting 264 weeks from the first IMP administration in LTS11210. In addition the patients will continue to be treated beyond 264 weeks until sarilumab is commercially available in their country or until 2020 at the latest when the study will be closed. *(In the UK the duration of treatment will be 264 weeks from the first study drug administration in LTS11210).* At the time of inclusion in this long-term extension, patients may have been exposed to sarilumab or placebo or active comparator for 2 to 52 weeks, depending on the study in which they were initially included. The sarilumab dose is reduced to 150 mg q2w in case of neutropenia, thrombocytopenia, or an increase in liver enzymes (alanine aminotransferase (ALT). A 12-week optional sub-study to evaluate the usability of pre-filled syringe with safety system (PFS-S) will be conducted in some countries. Patients in selected sites in those countries may be offered the opportunity to participate in this PFS-S sub-study.
STUDY POPULATION **Main selection criteria:**	**Inclusion criteria** Patients with RA who were randomized: • in the study EFC11072 (a randomized, double-blind, placebo-controlled study in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy) - and who have completed Part A (12 weeks) or Part B (52 weeks) of the study EFC11072. - or patients randomized in Part B of EFC11072 to a treatment arm subsequently not retained following pivotal dose selection. • in the study ACT11575 and completed the treatment period. • in the study EFC10832 - and completed the 24-week study treatment period. - or patients from 12 weeks onward with per protocol-defined lack of efficacy • in the study SFY13370 and completed the treatment period • in the study EFC13752 and completed the treatment period **Exclusion criteria** – Patients with any adverse event leading to permanent study drug (active or placebo) discontinuation in a prior study

	– Patients with an abnormality(ies) or adverse event(s) that per investigator judgment would adversely affect participation of the patient in the study
Total expected number of patients:	Maximum number of patients = Approximately 2000 patients.
Expected number of sites:	Approximately 400 sites
STUDY TREATMENT(s)	
Investigational Medicinal Product(s) **Formulation**	Sarilumab (anti-Interleukin 6Rα monoclonal antibody (Anti-IL6Rα mAb) Two different pharmaceutical forms are used in the study: C1F2 used in vials and C2F3 (pivotal formulation) used in prefilled syringes. **Before Phase 3 pivotal dose selection decision**: vials 150 mg (75 mg/ml) **After Phase 3 pivotal dose selection decision, and prior to availability of prefilled syringes**: vials 150 mg (75 mg/mL), and 200 mg (100 mg/mL) **After Phase 3 pivotal dose selection decision, upon availability of prefilled syringes:** prefilled syringes filled with 150 mg (131.6 mg/ml) or 200 mg (175 mg/ml) of drug product **In the sub-study:** prefilled syringes with a needle safety shield (PFS-S) with exactly the same IMP formulation as the PFS used in the main study
Route(s) of administration:	Subcutaneous (SC) injection in the abdomen, thigh, or upper arm Injection volume: 2 mL (vials); 1.14 mL (prefilled syringes)
Dose regimen:	Before the phase 3 pivotal dose selection decision, the sarilumab dose was 150 mg weekly (qw) (dose reduction to 150 mg q2w in case of neutropenia, thrombocytopenia, or an increase in liver enzymes (ALT). After the phase 3 pivotal doses were selected; the sarilumab dose is 200 mg q2w and the reduced dose is 150 mg q2w. Note: Patients enrolled in the study prior to the dose selection decision and receiving 150 mg qw were switched to 200 mg q2w. Patients who prior to the dose selection decision were assigned to the step-down dose of 150 mg q2w because of a safety issue continued to receive sarilumab 150 mg q2w.
Noninvestigational Medicinal Products (except EFC13752 patients)	One or a combination of non-biologic disease modifying drugs (DMARDs). Folic/Folinic acid in patients using MTX. Formulation, route of administration and dose regimen should follow the applicable local labeling information.
PRIMARY AND SECONDARY ENDPOINT(S)	**Primary endpoint:** Safety assessment of sarilumab over time. **Secondary Endpoint(s):** • The proportion of patients who achieve American College of Rheumatology criteria ACR20/ACR50/ACR70, DAS28 (Disease activity score) Remission, and EULAR (European League against Rheumatism) Response over time. • DAS28-CRP over time

	• HAQ-DI (Health assessment questionnaire – Disability index) results over time. • Van der Heijde modified total Sharp score over time and incidence of radiographic progression of the van der Heijde modified total Sharp score for the subset of patients who previously completed study EFC11072, Part B (Cohort 2 and Cohort 1 selected dose arms). • Each component of the ACR over time. • Health economic endpoints and Patient reported outcomes: patients will continue in evaluation of the health economic endpoints as per the initial study.
ASSESSMENT SCHEDULE	The last visit (EOT visit) of EFC11072, ACT11575, EFC10832, SFY13370, or EFC13752 will be used as the initial LTS11210 visit. All patients who agree to participate in the LTS11210 will need to sign a new informed consent form specific for this study. At D_1, after confirmation of eligibility, patients will be enrolled in the LTS11210 study. Patients will have site visits at weeks 4, 8, and 12, then every 12 weeks until the 2nd year of treatment in the study (Week 96). After 2 years of study participation, safety assessment and laboratory tests will take place at 24-week intervals. In addition, there will be visits at 24-week intervals in between regular study visits for distribution of IMP kits and recording of AEs only (*in Portugal and Sweden, hematology and liver function test evaluations will be performed at all IMP dispensing visits until end of treatment*) . After 264 weeks in LTS11210, some assessments will no longer be required in either scheduled visits or EOT visit (see Section 1.2). Additional laboratory testing (central) including hematology and liver function tests will be performed at week 2, week 6, and week 10 (site or home visits). Efficacy assessments will be performed at Weeks 0, 4, 8, 12 and then every 12 weeks up to Week 96 and then every 24 weeks until the end of treatment. Health economic assessments and Patient Reported outcomes (PROs) defined per initial study will be performed every 12 weeks up to Week 96 and then every 24 weeks until Week 264. PROs will not be assessed after Week 264, including EOT if EOT is after Week 264. Patients who completed EFC11072 Part B will have an additional X-ray evaluation at week 48, 96, 144, 192 (±14 days for each evaluation) or at EOT if EOT prior to Week 192. Electrocardiograms (ECGs) will be performed at the initial visit, week 48, 96, 144, 192, 240 and 264 or EOT. ECGs will not be performed after Week 264, including EOT if EOT is after Week 264. Adverse events will be collected throughout the study. Pharmacokinetic samples will be collected at V1 or V1/V2, V4 (Week 4), V7 (Week 12), every 12 weeks thereafter through year 2 and then every 24 weeks until the end of treatment and at the Post-Treatment follow-up visit 6 weeks after the end of treatment.

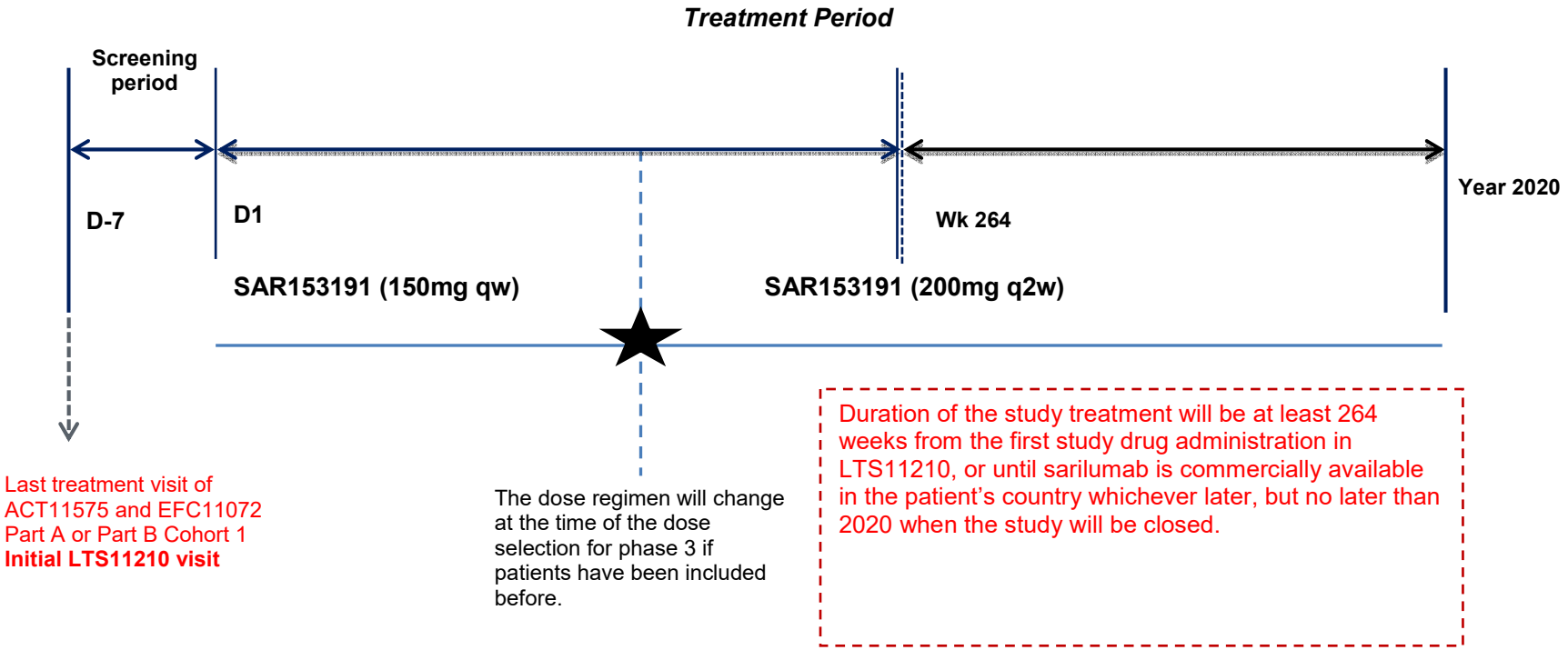
	Specific serum samples will be taken during the study to test for anti-drug antibody to sarilumab at week 12, every 12 weeks thereafter through year 2 and then every 24 weeks until the end of treatment and at the Post-Treatment follow-up visit 6 weeks after the end of treatment. Serum samples to store for future biomarker analyses will be collected at the initial visit, week 2, 12, and 48 (except for EFC13752 patients). Whole blood to store for future ribonucleic acid (RNA) expression analysis will be collected at week 0 (baseline) and week 2, except for patients from study SFY13370 and EFC13752. There will be a 6-week post treatment observation period for patients with early discontinuation and for patients who completed the planned treatment period. In patients who complete sarilumab treatment per protocol in countries where sarilumab is commercially available the post treatment follow-up visit may be cancelled if the patient initiates treatment with commercial sarilumab during the post treatment follow-up period. However, in this case, a telephone contact must be established with the patient to capture all AEs occurring up to the 1st administration of commercial sarilumab.
STATISTICAL CONSIDERATIONS	**Patient Population:** The primary analysis population will be safety population which is defined as all patients who have received at least one dose of treatment. **Analysis Methods:** The safety analyses will be based on the reported adverse events, clinical laboratory evaluations, vital signs, and 12-lead ECGs. The number and proportion of patients who experience an adverse event will be summarized by treatment group. Other categorical variables will be described in the same way. Continuous variables will be described using the mean, standard deviation, median, minimum and maximum. All summaries will be based on observed cases only; missing response data will not be imputed. For efficacy variables, descriptive statistics will be provided and 95% confidence intervals will be calculated if appropriate. Descriptive statistics will be provided for the van der Heijde modified total Sharp score for the subset of patients who previously completed study EFC11072, Part B. Data analysis results for patients who roll over from the EFC13752 study will be presented separately as sarilumab is administered as monotherapy in the EFC13752 and these patients will continue to be on sarilumab monotherapy in the LTS11210 study.
DURATION OF STUDY PERIOD (per patient)	Duration of the study treatment will be at least 264 weeks from the first study drug administration in LTS11210, or until sarilumab is commercially available in the patient's country whichever later, but no later than 2020 when the study will be closed. *(In the UK the duration of treatment will be 264 weeks from the first study drug administration in LTS11210).* The maximum duration of the study is expected to be approximately 523 weeks: Up to 1-week of screening, if any

	Up to 516-week open label treatment phase (for the earliest patients enrolled in LTS11210 in 2010 if sarilumab is not commercialized by 2020) 6-week post-treatment follow-up as required by the protocol

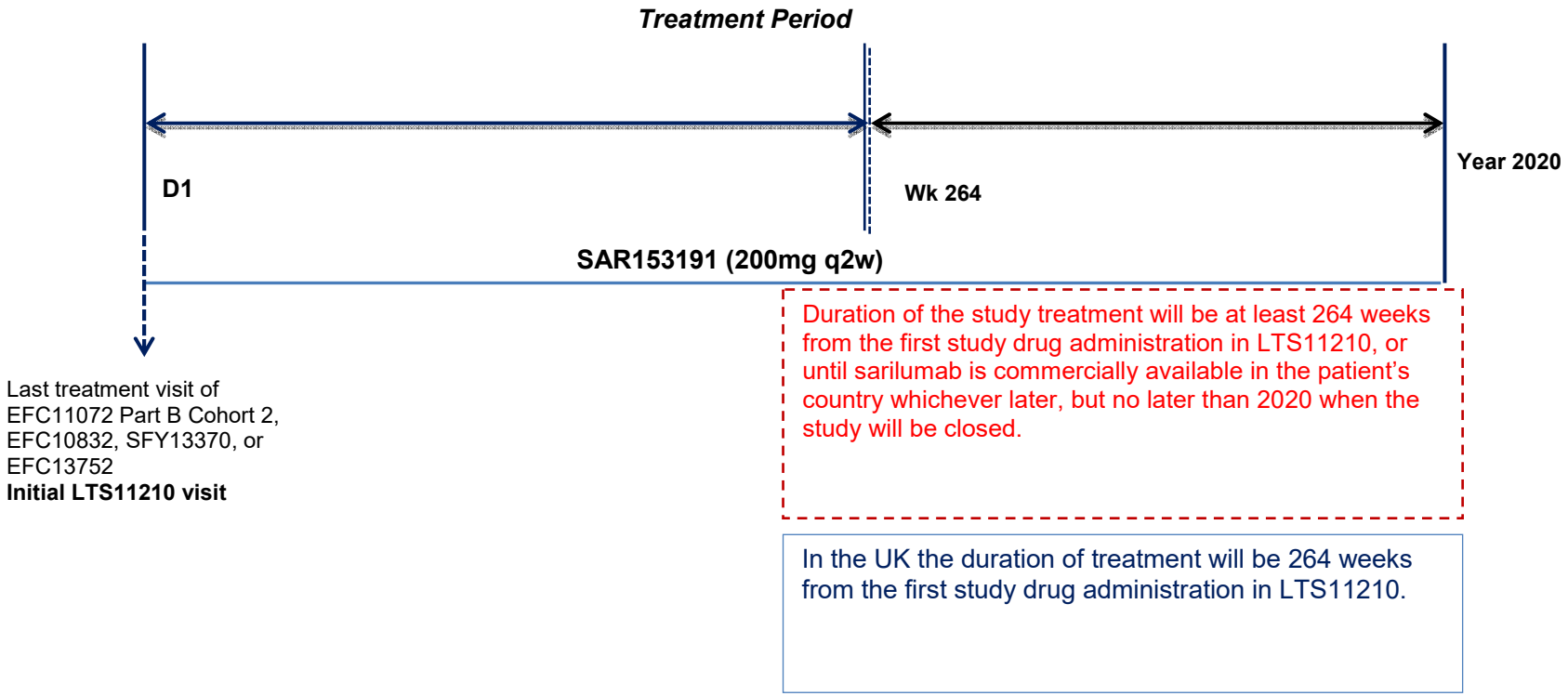
1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN

1.1.1 Graphical Study Design for Patients in ACT11575 and EFC11072 Part A or Part B Cohort 1



1.1.2 Graphical Study Design for Patients in EFC11072 Part B Cohort 2, EFC10832, SFY13370, and EFC13752



1.2 STUDY FLOWCHART

1.2.1 Study Flow Chart for Patients Enrolling From ACT11575 and EFC11072 Part A or Part B Cohort 1

Evaluation	Screening	Open Label Treatment												Post Treatment follow-up
DAY Week	Day -7 to D-1	Day 1 Wk0	Day 15 Wk 2	Day 29 Wk 4	Day 43 Wk 6	Day 57 Wk 8	Day 71 Wk 10	D85 Wk 12	Wk 24-96 (every 12 wks) Wk24, 36, 48, 60, 72, 84, 96	Wk 108- 492 IMP dispensing visits (every 24 weeks) Wk108, 132, 156, 180, 204, 228…492[a]	Wk120 – 264 (every 24 weeks) Wk120, 144, 168, 192, 216, 240, 264[a]	Wk288 – 504 (every 24 weeks) Wk 288, 312, …, 504[a]	EOT visit[a]	6 weeks after end of treatment[a] Post treatment follow-up
Visit no.	V 1 D-7 to D-1	V 2	HV 3[c] (± 3 days)	V 4 (±3 days)	HV 5[c] (±3 days)	V 6 (±3 days)	HV 6.1[c] (±3 days)	V 7 (±3 days)	V 8 to V 14 (±3 days)	V15, V17, V19, V21, V23, V25…V47(±3 days)	V16, V18, V20, V22, V24, V26 V28(±3 days)	V30, V32, V34, V36, V38, …, 48(±3 days)	V49 (±3 days)	V50(±3 days)
Design														
Inclusion/exclusion criteria	X	X												
Previous medical/surgical history	X													
Informed consent	X													
Patient demography	X													
Prior medication history	X													
Smoking, alcohol, and illicit drug use history	X													

Evaluation	Screening	Open Label Treatment												Post Treatment follow-up
DAY Week	Day -7 to D-1	Day 1 Wk0	Day 15 Wk 2	Day 29 Wk 4	Day 43 Wk 6	Day 57 Wk 8	Day 71 Wk 10	D85 Wk 12	Wk 24-96 (every 12 wks) Wk24, 36, 48, 60, 72, 84, 96	Wk 108- 492 IMP dispensing visits (every 24 weeks) Wk108, 132, 156, 180, 204, 228…492[a]	Wk120 – 264 (every 24 weeks) Wk120, 144, 168, 192, 216, 240, 264[a]	Wk288 – 504 (every 24 weeks) Wk 288, 312, …, 504[a]	EOT visit[a]	6 weeks after end of treatment[a] Post treatment follow-up
Visit no.	V 1 D-7 to D-1	V 2	HV 3[c] (± 3 days)	V 4 (±3 days)	HV 5[c] (±3 days)	V 6 (±3 days)	HV 6.1[c] (±3 days)	V 7 (±3 days)	V 8 to V 14 (±3 days)	V15, V17, V19, V21, V23, V25…V47(±3 days)	V16, V18, V20, V22, V24, V26 V28(±3 days)	V30, V32, V34, V36, V38, …, 48(±3 days)	V49 (±3 days)	V50(±3 days)
Detail history for tuberculosis (TB) and opportunistic infection	X													
Physical examination[e]	X[d]								X		X	X	X	
Confirm eligibility	X	X												
Treatment														
Study drug dispensing[b]		X		X		X		X	X	X	X	X		
Study drug compliance[b]				X		X		X	X	X	X	X	X	
Concomitant medications	X	X		X		X		X	X	X	X	X	X	X
Vital signs														
Temperature, heart rate, blood pressure	X[d]	X		X		X		X	X		X	X	X	X
Weight in Kg	X[d]	X		X		X		X	X		X	X	X	X

Evaluation	Screening	Open Label Treatment												Post Treatment follow-up
DAY Week	Day -7 to D-1	Day 1 Wk0	Day 15 Wk 2	Day 29 Wk 4	Day 43 Wk 6	Day 57 Wk 8	Day 71 Wk 10	D85 Wk 12	Wk 24-96 (every 12 wks) Wk24, 36, 48, 60, 72, 84, 96	Wk 108- 492 IMP dispensing visits (every 24 weeks) Wk108, 132, 156, 180, 204, 228…492[a]	Wk120 – 264 (every 24 weeks) Wk120, 144, 168, 192, 216, 240, 264[a]	Wk288 – 504 (every 24 weeks) Wk 288, 312, …, 504[a]	EOT visit[a]	6 weeks after end of treatment[a] Post treatment follow-up
Visit no.	V 1 D-7 to D-1	V 2	HV 3[c] (± 3 days)	V 4 (±3 days)	HV 5[c] (±3 days)	V 6 (±3 days)	HV 6.1[c] (±3 days)	V 7 (±3 days)	V 8 to V 14 (±3 days)	V15, V17, V19, V21, V23, V25…V47(±3 days)	V16, V18, V20, V22, V24, V26 V28(±3 days)	V30, V32, V34, V36, V38, …, 48(±3 days)	V49 (±3 days)	V50(±3 days)
Efficacy														
ACR disease core set[h]	X[d]	X		X		X		X	X		X	X	X	
X-ray (hand, feet)[g]	X[d]								X		X		X	
Health Economic														
SF-36	X[d]							X	X		X		X[f]	
WPAI	X[d]							X	X		X		X[f]	
FACIT-Fatigue, Sleep questionnaire	X[d]							X	X		X		X[f]	
Safety														
Tuberculosis assessments	X[d]	X		X		X		X	X		X	X	X	X
AE/SAE recording (if any)	←													→
Laboratory Testing														
High sensitive- C-Reactive protein (hs-CRP)	X[d]	X		X		X		X	X		X	X	X	

Evaluation	Screening	Open Label Treatment												Post Treatment follow-up
DAY Week	Day -7 to D-1	Day 1 Wk0	Day 15 Wk 2	Day 29 Wk 4	Day 43 Wk 6	Day 57 Wk 8	Day 71 Wk 10	D85 Wk 12	Wk 24-96 (every 12 wks) Wk24, 36, 48, 60, 72, 84, 96	Wk 108- 492 IMP dispensing visits (every 24 weeks) Wk108, 132, 156, 180, 204, 228…492[a]	Wk120 – 264 (every 24 weeks) Wk120, 144, 168, 192, 216, 240, 264[a]	Wk288 – 504 (every 24 weeks) Wk 288, 312, …, 504[a]	EOT visit[a]	6 weeks after end of treatment[a] Post treatment follow-up
Visit no.	V 1 D-7 to D-1	V 2	HV 3[c] (± 3 days)	V 4 (±3 days)	HV 5[c] (±3 days)	V 6 (±3 days)	HV 6.1[c] (±3 days)	V 7 (±3 days)	V 8 to V 14 (±3 days)	V15, V17, V19, V21, V23, V25…V47(±3 days)	V16, V18, V20, V22, V24, V26 V28(±3 days)	V30, V32, V34, V36, V38, …, 48(±3 days)	V49 (±3 days)	V50(±3 days)
Hematology: CBC and differential[i]	X[d]	X	X	X	X	X	X	X	X		X	X	X	
Liver Function Tests (LFTs)[j]	X[d]	X	X	X	X	X	X	X	X		X	X	X	
Lipids (fasting)[k]	X[d]			X		X		X	X		X	X	X	
Clinical chemistry (fasting)[l]	X[d]					X		X	X		X	X	X	
ANA/Anti-ds-DNA[m]	X[d]								X		X	X	X	
Dipstick urinalysis [n]	X[d]					X		X	X		X		X[f]	
Urine pregnancy test (for women of childbearing potential)[o]	X[d]			X		X		X	X		X	X	X	X
Dispense urine pregnancy kits [o]								X	X		X	X		
12-lead electrocardiogram [p]	X[d]								X		X		X[f]	

Evaluation	Screening	Open Label Treatment												Post Treatment follow-up
DAY Week	Day -7 to D-1	Day 1 Wk0	Day 15 Wk 2	Day 29 Wk 4	Day 43 Wk 6	Day 57 Wk 8	Day 71 Wk 10	D85 Wk 12	Wk 24-96 (every 12 wks) Wk24, 36, 48, 60, 72, 84, 96	Wk 108- 492 IMP dispensing visits (every 24 weeks) Wk108, 132, 156, 180, 204, 228…492[a]	Wk120 – 264 (every 24 weeks) Wk120, 144, 168, 192, 216, 240, 264[a]	Wk288 – 504 (every 24 weeks) Wk 288, 312, …, 504[a]	EOT visit[a]	6 weeks after end of treatment[a] Post treatment follow-up
Visit no.	V 1 D-7 to D-1	V 2	HV 3[c] (± 3 days)	V 4 (±3 days)	HV 5[c] (±3 days)	V 6 (±3 days)	HV 6.1[c] (±3 days)	V 7 (±3 days)	V 8 to V 14 (±3 days)	V15, V17, V19, V21, V23, V25…V47(±3 days)	V16, V18, V20, V22, V24, V26 V28(±3 days)	V30, V32, V34, V36, V38, …, 48(±3 days)	V49 (±3 days)	V50(±3 days)
Other analysis														
Rheumatoid factor[q]		X							X		X		X[f]	
Serum IL-6 [v]	X[d]			X				X	X					
Pharmacokinetics [r]	X[d]			X				X	X		X	X	X	X
Anti-sarilumab antibody	X[d]							X	X		X	X	X	X
Serum sample to be stored for future biomarkers [s]	X[d]		X					X	X					
Expression RNA [t]		X[d]	X											

a EOT visit and follow up visit 6 weeks later should be completed for all patients at the end of treatment (in patients who complete sarilumab treatment per protocol in countries where sarilumab is commercially available the post treatment follow-up visit may be cancelled if the patient initiates treatment with commercial sarilumab during the post treatment follow-up period; however, in this case, a telephone contact must be established with the patient to capture all AEs occurring up to the 1st administration of commercial sarilumab). EOT visit may occur when the patients complete 264 weeks of sarilumab treatment from the LTS11210, or at any visit thereafter when sarilumab is commercialized in their country, but no later than 2020 when the study will be closed. In case of permanent discontinuation of treatment, the patients will be assessed using the procedures normally planned for the EOT visit and the 6 week follow up visit 6 weeks later.

b From Week 24, patients at limited sites in selected countries may participate in PFS-S sub-study. If the patient enters the sub-study, then the sub-study IMP will be dispensed instead of the main study IMP at the entry into sub-study and IMP compliance with sub-study IMP will be reviewed at the end of sub-study. Full details of the sub-study are provided in Appendix R

c HV: Visit can be home visit or clinic visit to draw and collect the blood sample only for hematology and LFTs using the designated central laboratory.

d Last treatment visit from the study EFC11072 or ACT11575. Please note that the SF-36 must be completed at the screening visit of the LTS11210 study for patients rolling over from EFC11072 Part A and ACT11575 studies. Please note that the RNA sample must be collected at V2 of the LTS11210 study for patients rolling over from EFC11072.

e Physical examination to be done at Week 48, 96, 144, 192, 240, 264, 288, 336, 384, 432, 480 and EOT visit.

f Assessment is NOT required when EOT visit is after Week 264.

g X-ray of hand and feet (only for patients who completed Part B of the study EFC11072 (not performed for Part A patients, or patients from Part B non-selected dose arms) will be done at Weeks 48, 96, 144, 192 (±14 days for each assessment), and EOT; No X-ray evaluation will be performed after Week 192 including EOT if EOT is after Week 192. Required x-ray must be done after confirmation of negative urine pregnancy test in women of child bearing potential.

h After Week 264, only DAS28 components of ACR core set will be assessed (TJC & SJC for 28 joints, patient´s global assessment of disease activity).

i Hematology: Hemoglobin, hematocrit, red blood cell (RBC) morphology (if blood cell count is abnormal), white blood cell (WBC) with differential, platelets count**.** For all patients, a CBC test must be performed before or at Visit 3 (using either designated central lab or a local laboratory facility), but not earlier than the 12th day after the first dose of IMP administration in order to confirm that the neutrophil count and platelet count are not within the protocol-defined limits for temporary or permanent discontinuation of study drug.

j Liver Function Tests (LFTs): Prothrombin Time (PT), Albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, conjugated bilirubin, unconjugated bilirubin. PT is NOT required at any visit after Week 264.

k Lipids (fasting): Total cholesterol (TC), High-Density Lipoprotein (HDL) cholesterol, Low-Density Lipoprotein (LDL) cholesterol, triglycerides, Apolipoprotein A, and Apolipoprotein B. After Week 264, lipids (excluding Apolipoprotein A, and Apolipoprotein B) will only be assessed at Weeks 288, 336, 384, 432, 480 (including EOT if EOT is after Week 264)

l Clinical chemistry (fasting): fasting glucose, total proteins, calcium, sodium, potassium, Lactate Dehydrogenase, (LDH), urea nitrogen and creatinine. Creatinine clearance will be calculated during the study if clinical indicated.

m ANA titer will be done at screening, at Week 48, 96, 144, 192, 240, 264, 288, 336, 384, 432, 480 and EOT visit or sooner if clinical indicated (Anti-ds-DNA only if ANA titer is >1:160)

n Dipstick urinalysis for: specific gravity, pH, glucose, blood, ketones, proteins, bilirubin, urobilinogen, nitrite, leukocytes. If any parameter is abnormal, a urinalysis sample should be sent to central laboratory for testing. If positive for proteins, microscopic analysis will be performed by central laboratory.

o After Visit 7 (Week 12) between study visits the patient will have a urine pregnancy test at home on a monthly basis. Patients will be given sufficient urine pregnancy kits to take home at each successive visit for monthly testing up until the final treatment visit. When the testing coincides with a clinical visit as indicated in the flow chart, the results should be reported in the eCRF. No pregnancy test kits will be dispensed at EOT.

p ECG to be done at Weeks 48, 96, 144, 192, 240, 264 or EOT; No ECG will be done after Week 264 including EOT if EOT is after Week 264.

q Rheumatoid factor only at baseline Visit 2 (Week 0) and at Weeks 48, 96, 144, 192, 240, 264 or EOT. No Rheumatoid factor will be assessed after Week 264 including EOT if EOT is after Week 264.

r If throughout the study a serious adverse event (SAE) occurs in a patient, blood samples should be collected for sarilumab at or near the onset and completion of the occurrence of the event, if possible. The exact date of sample collection and last dose must be recorded on the e-CRF.

s Serum sample for biomarkers to be collected at screening (ie, the last treatment visit from the EFC11072 or ACT11575), Week 2, Week 12, and Week 48.

t Blood sample for RNA to be collected at Week 0 (baseline, prior to administration of study drug) and Week 2 (at site visit only; cancel RNA collection if home visit).

u Deleted.

v Samples for IL-6 to be collected at Screening (ie the last treatment visit from EFC11072 or ACT11575) and at V4 (Week 4), V7 (Week 12), V8 (Week 24), V9 (Week 36), and V10 (Week 48).

1.2.2 Study Flow Chart for Patients Enrolling From EFC10832, EFC11072 Part B Cohort 2, SFY13370, and EFC13752

Evaluation	Open Label Treatment												Post Treatment follow-up
DAY and/or WEEK	Day 1 WK0	Day 15 Wk 2	Day 29 Wk 4	Day 43 Wk 6	Day 57 Wk 8	Day 71 Wk 10	D85 Wk 12	Wk 24-96 (every 12 wks) Wk 24, 36, 48, 60, 72, 84, 96	Wk 108-492IMP dispensing visits (every 24 weeks) Wk108, 132, 156, 180, 204, 228… 492[a]	Wk120 – 264 (every 24 weeks) Wk120, 144, 168, 192, 216, 240, 264[a]	Wk288 – 504 (every 24 weeks) Wk288, 312,…, 504[a]	EOT visit[a]	6 weeks after end of treatment[a] Post treatment follow-up
Visit no.	V1/V 2	HV 3[c] (± 3 days)	V 4 (±3 days)	HV 5[c] (±3 days)	V 6 (±3 days)	HV 6.1[c] (±3 days)	V 7 (±3 days)	V 8 to V14~~28~~ (±3 days)	V15, V17, V19, V21, V23, V25… V47 (±3 days)	V16, V18, V20, V22, V24, V26, V28 (±3 days)	V30, V32, V34, V36, V38, … , V48 (±3 days)	V49 (±3 days)	V50(±3 days)
Design													
Inclusion/exclusion criteria	X												
Previous medical/surgical history	X												
Informed consent	X												
Patient demography	X												
Prior medication history	X												
Smoking, alcohol, and illicit drug use history	X												
Detail history for tuberculosis (TB) and opportunistic infection	X												
Physical examination[e]	X[d]							X		X	X	X	
Confirm eligibility	X												

Evaluation	Open Label Treatment												Post Treatment follow-up
DAY and/or WEEK	**Day 1** **WK0**	**Day 15** **Wk 2**	**Day 29** **Wk 4**	**Day 43** **Wk 6**	**Day 57** **Wk 8**	**Day 71** **Wk 10**	**D85** **Wk 12**	**Wk 24-96** **(every 12 wks)** **Wk 24, 36, 48, 60, 72, 84, 96**	**Wk 108-492IMP dispensing visits** **(every 24 weeks)** **Wk108, 132, 156, 180, 204, 228… 492[a]**	**Wk120 – 264** **(every 24 weeks)** **Wk120, 144, 168, 192, 216, 240, 264[a]**	**Wk288 – 504** **(every 24 weeks)** **Wk288, 312,…, 504[a]**	**EOT visit[a]**	**6 weeks after end of treatment[a]** **Post treatment follow-up**
Visit no.	**V1/V 2**	**HV 3[c] (± 3 days)**	**V 4 (±3 days)**	**HV 5[c] (±3 days)**	**V 6 (±3 days)**	**HV 6.1[c] (±3 days)**	**V 7 (±3 days)**	**V 8 to V14~~28~~ (±3 days)**	**V15, V17, V19, V21, V23, V25… V47 (±3 days)**	**V16, V18, V20, V22, V24, V26, V28 (±3 days)**	**V30, V32, V34, V36, V38, … , V48 (±3 days)**	**V49 (±3 days)**	**V50(±3 days)**
Treatment													
Study drug dispensing[b]	X		X		X		X	X	X	X	X		
Study drug compliance[b]			X		X		X	X	X	X	X	X	
Concomitant medications	X		X		X		X	X	X	X	X	X	X
Vital signs													
Temperature, heart rate, blood pressure	X[d]		X		X		X	X		X	X	X	X
Weight in Kg	X[d]		X		X		X	X		X	X	X	X
Efficacy													
ACR disease core set[h]	X[d]		X		X		X	X		X	X	X	
X-ray (hand, feet)[g]	X[d]							X		X		X	
Health Economic													
SF-36 (EFC11072, EFC10832)	X[d]						X	X		X		X[f]	
WPAI (EFC11072)	X[d]						X	X		X		X[f]	
FACIT-Fatigue (EFC11072, EFC10832)	X[d]						X	X		X		X[f]	
Sleep questionnaire (EFC11072)	X[d]						X	X		X		X[f]	

Evaluation	Open Label Treatment												Post Treatment follow-up
DAY and/or WEEK	Day 1 WK0	Day 15 Wk 2	Day 29 Wk 4	Day 43 Wk 6	Day 57 Wk 8	Day 71 Wk 10	D85 Wk 12	Wk 24-96 (every 12 wks) Wk 24, 36, 48, 60, 72, 84, 96	Wk 108-492IMP dispensing visits (every 24 weeks) Wk108, 132, 156, 180, 204, 228… 492[a]	Wk120 – 264 (every 24 weeks) Wk120, 144, 168, 192, 216, 240, 264[a]	Wk288 – 504 (every 24 weeks) Wk288, 312,…, 504[a]	EOT visit[a]	6 weeks after end of treatment[a] Post treatment follow-up
Visit no.	V1/V 2	HV 3[c] (± 3 days)	V 4 (±3 days)	HV 5[c] (±3 days)	V 6 (±3 days)	HV 6.1[c] (±3 days)	V 7 (±3 days)	V 8 to V14~~28~~ (±3 days)	V15, V17, V19, V21, V23, V25… V47 (±3 days)	V16, V18, V20, V22, V24, V26, V28 (±3 days)	V30, V32, V34, V36, V38, … , V48 (±3 days)	V49 (±3 days)	V50(±3 days)
WPS-RA (EFC10832)	X[d]						X	X		X		X[f]	
Safety													
Tuberculosis assessments	X[d]		X		X		X	X		X	X	X	X
AE/SAE recording (if any)	←												→
Laboratory Testing													
High sensitive- C- Reactive protein (hs-CRP)	X[d]		X		X		X	X		X	X	X	
Hematology: CBC and differential[i]	X[d]	X	X	X	X	X	X	X		X	X	X	
Liver Function Tests (LFTs)[j]	X[d]	X	X	X	X	X	X	X		X	X	X	
Lipids (fasting)[k]	X[d]		X		X		X	X		X	X	X	
Clinical chemistry (fasting)[l]	X[d]				X		X	X		X	X	X	
ANA/Anti-ds-DNA [n]	X[d]							X		X	X	X	
Dipstick urinalysis [o]	X[d]				X		X	X		X		X[f]	
Urine pregnancy test (for women of childbearing potential)[p]	X[d]		X		X		X	X		X	X	X	X

Evaluation	Open Label Treatment												Post Treatment follow-up
DAY and/or WEEK	**Day 1** **WK0**	**Day 15** **Wk 2**	**Day 29** **Wk 4**	**Day 43** **Wk 6**	**Day 57** **Wk 8**	**Day 71** **Wk 10**	**D85** **Wk 12**	**Wk 24-96** **(every 12 wks)** **Wk 24, 36, 48, 60, 72, 84, 96**	**Wk 108-492IMP dispensing visits** **(every 24 weeks)** **Wk108, 132, 156, 180, 204, 228… 492[a]**	**Wk120 – 264** **(every 24 weeks)** **Wk120, 144, 168, 192, 216, 240, 264[a]**	**Wk288 – 504** **(every 24 weeks)** **Wk288, 312,…, 504[a]**	**EOT visit[a]**	**6 weeks after end of treatment[a]** **Post treatment follow-up**
Visit no.	**V1/V 2**	**HV 3[c] (± 3 days)**	**V 4 (±3 days)**	**HV 5[c] (±3 days)**	**V 6 (±3 days)**	**HV 6.1[c] (±3 days)**	**V 7 (±3 days)**	**V 8 to V1428 (±3 days)**	**V15, V17, V19, V21, V23, V25… V47 (±3 days)**	**V16, V18, V20, V22, V24, V26, V28 (±3 days)**	**V30, V32, V34, V36, V38, … , V48 (±3 days)**	**V49 (±3 days)**	**V50(±3 days)**
Dispense urine pregnancy kits[p]							X	X		X	X		
12-lead electrocardiogram[q]	X[d]							X		X		X[f]	
Other analysis													
Rheumatoid factor[r]	X[d]							X		X		X[f]	
Serum IL-6 [w]	X		X				X	X					
Pharmacokinetics[s]	X[d]		X				X	X		X	X	X	X
Anti-sarilumab antibody	X[d]						X	X		X	X	X	X
Serum sample to be stored for future biomarkers [t]	X[d]	X					X	X					
Expression RNA[u]	X	X											

a EOT visit and follow up visit 6 weeks later should be completed for all patients at the end of treatment (in patients who complete sarilumab treatment per protocol in countries where sarilumab is commercially available the post treatment follow-up visit may be cancelled if the patient initiates treatment with commercial sarilumab during the post treatment follow-up period; however, in this case, a telephone contact must be established with the patient to capture all AEs occurring up to the 1st administration of commercial sarilumab). EOT visit may occur when the patients complete 264 weeks of sarilumab treatment from LTS11210, or any visit thereafter when sarilumab is commercialized in their country, but no later than 2020 when the study will be closed. *(In UK, the duration of treatment will be 264 weeks from the first study drug administration in LTS11210).* In case of permanent discontinuation of treatment, the patients will be assessed using the procedures normally planned for the EOT visit and the 6 week follow up visit 6 weeks later.

b From Week 24, patients at limited sites in selected countries may participate in PFS-S sub-study. If the patient enters the sub-study, then the sub-study IMP will be dispensed instead of the main study IMP at the entry into sub-study and IMP compliance with sub-study IMP will be reviewed at the end of sub-study. Full details of the sub-study are provided in Appendix R

c HV: Visit can be home visit or clinic visit to draw and collect the blood sample only for hematology and LFTs using the designated central laboratory.

d Last treatment visit from the study EFC11072, EFC10832, SFY13370, or EFC13752.

e Physical examination to be done at Week 48, 96, 144, 192, 240, 264, 288, 336, 384, 432, 480 and EOT visit

f The assessment is NOT required when EOT visit is after Week 264.

g X-ray of hands and feet (only for patients who completed Part B of the study EFC11072 will be done at Weeks 48, 96, 144, 192 (±14 days for each assessment), and EOT; No X-ray evaluation will be performed after Week 192 including EOT if EOT is after Week 192. Required x-ray must be done after confirmation of negative urine pregnancy test in women of child bearing potential.

h After Week 264, only DAS28 components of ACR core set will be assessed (TJC & SJC for 28 joints, patient´s global assessment of disease activity).

i Hematology: Hemoglobin, hematocrit, red blood cell (RBC) morphology (if blood cell count is abnormal), white blood cell (WBC) with differential, platelets count. For all patients, a CBC test must be performed before or at Visit 3 (using either designated central or a local laboratory facility) but not earlier than the 12th day after the first dose of IMP administration in order to confirm that the neutrophil count and platelet count are not within the protocol-defined limits for temporary or permanent discontinuation of study drug.

j Liver Function Tests (LFTs): Prothrombin Time (PT), Albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, conjugated bilirubin, unconjugated bilirubin. PT is NOT required at any visit after Week 264.

k Lipids (fasting): Total cholesterol (TC), High-Density Lipoprotein (HDL) cholesterol, Low-Density Lipoprotein (LDL) cholesterol, triglycerides, Apolipoprotein A, and Apolipoprotein B. After Week 264, lipids (excluding Apolipoprotein A, and Apolipoprotein B) will only be assessed at Weeks 288, 336, 384, 432, 480 (including EOT if EOT is after Week 264)

l Clinical chemistry (fasting): fasting glucose, total proteins, calcium, sodium, potassium, Lactate Dehydrogenase, (LDH), urea nitrogen and creatinine. Creatinine clearance will be calculated during the study if clinical indicated.

m Deleted.

n ANA titer will be done at V1/V2 (ie the last treatment visit from the initial study), at Week 48, 96, 144, 192, 240, 264, 288, 336, 384, 432, 480 and EOT visit , or sooner if clinical indicated (Anti-ds-DNA only if ANA titer is >1:160)

o Dipstick urinalysis for: specific gravity, pH, glucose, blood, ketones, proteins, bilirubin, urobilinogen, nitrite, leukocytes. If any parameter is abnormal, a urinalysis sample should be sent to central laboratory for testing. If positive for proteins, microscopic analysis will be performed by central laboratory.

p After Visit 7 (Week 12) between study visits the patient will have a urine pregnancy test at home on a monthly basis. Patients will be given sufficient urine pregnancy kits to take home at each successive visit for monthly testing up until the final treatment visit. When the testing coincides with a clinical visit as indicated in the flow chart, the results should be reported in the e-CRF. No pregnancy test kits will be dispensed at EOT.

q ECG to be done at Weeks 48, 96, 144, 192, 240, 264 or EOT; No ECG will be done after Week 264 including EOT if EOT is after Week 264

r Rheumatoid factor only at Weeks 48, 96, 144, 192, 240, 264 or EOT; No Rheumatoid factor will be assessed after Week 264 including EOT if EOT is after Week 264

s If throughout the study a serious adverse event (SAE) occurs in a patient, blood samples should be collected for sarilumab at or near the onset and completion of the occurrence of the event, if possible. The exact date of sample collection and last dose must be recorded on the eCRF.

t Serum sample for biomarkers to be collected for all patients except EFC13752: at V1/V2 (ie, the last treatment visit from the initial study), as well as Week 2, Week 12, and Week 48.

u Blood sample for RNA except for SFY13370 and EFC13752 patients: to be collected at V1/V2 (Week 0) (baseline prior to administration of study drug) and V3 (Week 2) at site visit only (cancel RNA collection if home visit).

v Deleted

w Samples for IL-6 to be collected at V1/V2 for EFC11072 patients only (ie the last treatment visit) and for all patients at V4 (Week 4), V7 (Week 12), V8 (Week 24), V9 (Week 36), and V10 (Week 48).

2 TABLE OF CONTENT

3 LIST OF ABBREVIATIONS

ACR:	American College of Rheumatology
ADA:	anti-drug antibody
AE:	Adverse Event
AEPM:	Adverse Event of Pre-specified Monitoring
AESI:	Adverse Event of Special Interest
ALP:	Alkaline Phosphatase
ALT:	Alanine Aminotransferase
ANA:	Anti Nuclear Auto antibody
Anti-ds DNA:	Anti double stranded DNA
AST:	Aspartate Aminotransferase
ATC:	Anatomic Category
CAC:	Cardiovascular Adjudication Committee
CBC:	Complete Blood Count
CIB:	Clinical Investigators Brochure
CV%:	Coefficient of Variation
CYP:	Cytochrome P450
DAS28:	disease activity score
DMARDs:	Disease Modifying Anti-Rheumatic Drugs
DNA:	DeoxyriboNucleic Acid
DRF:	Discrepancy Resolution Form
ds-DNA:	double-standard DNA
ECG:	Electrocardiogram
e-CRF:	electronic Case Report Form
EULAR:	European League against Rheumatism
FACIT-Fatigue:	Functional Assessment of Chronic Illness Therapy Fatigue scale
FDD:	failed drug deliveries
HDL:	High Density Lipoprotein
HLGT:	High Level Group Term
HLT:	High Level Term
hs-CRP:	high sensitivity C-reactive protein, high sensitivity C-reactive protein
ICH:	International Conference on Harmonisation
IECs/IRBs:	Independent Ethic Committees/Institutional Review Board
IL-6:	interleukin 6
IL6 R mAB:	Interleukin 6 Receptor monoclonal Antibody
IMP:	investigational medicinal product
IUD:	*Intra Uterine Device*
IVRS:	Interactive Voice Response System
IWRS:	Interactive Web Response System
kDa:	Kilodalton
LDH:	Lactacte Dehydrogenase
LDL:	Low Density Lipoprotein

LLN:	Lower Limit of Normal
MedDRA:	Medical Dictionary for Regulatory Activities
NIMP:	noninvestigational medicinal product
NSAIDs:	Non Steroidal Anti-Inflammatory Drugs
PCSA:	Potentially Clinically Significant Abnormality
PFS-S:	pre-filled syringe with safety system, pre-filled syringe with safety system
PK:	Pharmacokinetic
PML:	Progressive Multifocal Leukoencephalopathy
PROs:	Patient Reported Outcomes, Patient Reported Outcomes
PT:	Preferred Term, Prothrombin Time
PTC:	product technical complaint
PTF:	product technical failure
q2w:	bi-weekly (every-other-week)
qw:	weekly
RA:	Rheumatoid Arthritis
RBC:	Red Blood Cells
RF:	Rheumatoid Factor
RNA:	Ribonucleic Acid
SAE:	Serious Adverse Event
SD:	Standard Deviation
SEM:	Standard Error of the Mean
SF-36:	Short Form 36
SJC:	Swollen Joints Count
SLE:	Systemic Lupus Erythematosus
SMQ:	Standardized MedDRA Query
SOC:	System Organ Class
SUSAR:	Suspected Unexpected Serious Adverse Reaction
TB:	Tuberculosis
TC:	total cholesterol
TEAEs:	Treatment Emergent Adverse Events
TJC:	Tender Joints Count
ULN:	Upper limit of normal
VAS:	Visual Analog Scale
WBC:	White Blood Cells
WICF:	Written Informed Consent Form, Written Informed Consent Form
WOCBP:	Women of Childbearing Potential
WPAI:	Work Productivity and Activity Impairment
WPS:	work productivity survey
WPS-RA:	Rheumatoid Arthritis-Work Productivity Survey

4 INTRODUCTION AND RATIONALE

Rheumatoid arthritis (RA) is a chronic, debilitating disease that primarily affects the synovial membrane of diarthrodial joints.

Currently, treatment of RA involves the use of nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease modifying anti-rheumatic drugs (DMARDs). Methotrexate, sulfasalazine, hydroxychloroquine and leflunomide are DMARDs that have been used by rheumatologists for many years (1)(2)(3).

Introduction of biologic agents, especially inhibitors of TNF-α, has greatly improved the therapeutic options available for treating RA (4)(5)(6)(7)(8)(9); however, no therapeutic modality provides either universal or complete control of disease and safety remains one of the key issues with anti-TNF-α treatment (10)(11).

Besides early benefit/risk of biologics, the long term outcome of RA remain a critical question: long term use of biologics have been associated with immunosuppression and effects on the development of infections, malignancies, demyelinating events, lupus like events, etc. Consequently, long-term data are needed to investigate the risks associated with the long-term use of these drugs.

This LTS11210 study is intended to identify potential late onset adverse events associated with long-term use of sarilumab with or without concomitant non-biologic DMARD(s), including MTX, as well as to assess long-term efficacy.

4.1 SARILUMAB

Sarilumab is a fully human immunoglobulin (Ig) G1 monoclonal antibody directed against the IL-6Rα receptor produced using VelocImmune® technology developed by Regeneron. Sarilumab blocks the IL6 receptor and inhibits IL-6 signaling. Sarilumab is under development for the treatment of patients with moderate to severe RA.

Sarilumab is a covalent heterotetramer consisting of two, disulfide linked human heavy chains, each covalently linked through disulfide bonds to a fully human kappa light chain. The antibody possesses a protein molecular weight of approximately 155 kDa, with a single N-linked glycosylation site in each heavy chain, located within the constant region in the Fc portion of the molecule. The sarilumab heavy chain has an IgG1 isotype constant region (an allotype). The variable domains of the heavy and light chains combine to form the IL-6Rα binding site within the antibody.

4.1.1 Summary of nonclinical studies

See the clinical investigator's brochure (CIB) for detailed information.

4.1.2 Summary of previous human experience

See the Clinical Investigator's Brochure for detailed information.

Prior to entering LTS11210 patients were included in ACT11575, EFC11072, EFC10832, SFY13370, or EFC13752.

In the initial studies patients were exposed to IMP for:

- 12 weeks if they were initially randomized in EFC11072 Part A or ACT11575;
- between 2 and 52 weeks, if initially randomized in EFC11072 Part B;
- between 12 and 24 weeks, if initially randomized in EFC10832;
- 24 weeks, if initially randomized in SFY13370 or EFC13752.

These studies are described briefly below:

EFC11072: A randomized, double-blind, placebo-controlled, multi-centre, two-part, dose ranging (Part A) and confirmatory (Part B) study with an operationally seamless design, evaluating efficacy and safety of sarilumab added to methotrexate (MTX) in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy. The study is completed.

In the dose ranging part of the study (Part A), five doses (100 mg weekly [qw], 150 mg qw, 100 mg every other week [q2w], 150 mg q2w, and 200 mg q2w) and placebo were tested in combination with methotrexate (MTX). Two doses (150 mg every two weeks [q2w] and 200 mg q2w) were selected for the pivotal phase 3 studies. In the Phase 3 confirmatory part (Part B) both sarillumab arms showed clinically relevant and statistically significant ($p<0.0001$) improvements compared with placebo in all 3 co-primary efficacy endpoints (signs and symptoms [American College of Rheumatology criteria, ACR20], physical function [Health Assessment Questionnaire Disability Index, HAQ-DI], and radiographic progression [modified van der Heijde total Sharp score, vdH-mTSS]). In this study, the safety profile was consistent with previous studies showing higher incidence of infections including serious infections, in the sarilumab treated groups compared to placebo, along with the expected laboratory data: a decrease in neutrophil count, elevated alanine aminotransferase, elevated serum LDL-cholesterol and injection site reactions (i.e., erythema, pruritus and rash). The incidence of treatment emergent anti-drug antibody (ADA) in the sarilumab 150 mg q2w, 200 mg q2w, and placebo groups were 19.8%, 14.6%, and 4.2%, with 3.5%, 2.4% and 0.2% of neutralizing ADA, respectively. No notable differences have been observed with regards to loss or lack of efficacy or hypersensitivity reactions, including systemic and local, between those patients who were ADA positive and ADA negative (see the Investigator's Brochure for details).

ACT11575: A randomized, double-blind, parallel-group, placebo- and active calibrator-controlled study assessing the clinical benefit of sarilumab on top of MTX in patients with active RA who have failed previous TNF-α antagonists was terminated by the Sponsor due to administrative reasons with only 16 patients enrolled.

The objective of ACT11575 was to demonstrate that sarilumab added to MTX is superior in efficacy to placebo, for the relief of signs and symptoms of RA, in patients with active RA who have failed up to 2 TNF-α antagonists.

EFC10832: A randomized, double-blind, parallel-group, placebo-controlled study assessing the efficacy and safety of sarilumab added to DMARD therapy in patients with active rheumatoid arthritis (RA) who are inadequate responders or intolerant to tumor necrosis factor-alpha (TNF-α) antagonists. The study is completed.

The objective of EFC10832 was to demonstrate that sarilumab added to DMARD therapy is superior in efficacy to placebo for the relief of signs and symptoms of RA at Week 24 in patients with active RA who are inadequate responders or intolerant to TNF-α antagonists.

SFY13370: A randomized, double-blind, double-dummy study assessing the safety and tolerability of sarilumab and tocilizumab in patients with rheumatoid arthritis who are inadequate responders to or intolerant of TNF antagonists. The study is completed.

The primary objective of SFY13370 was to assess, in the same study, the safety of sarilumab and tocilizumab in patients with rheumatoid arthritis (RA) who are inadequate responders to or intolerant of tumor necrosis factor (TNF) antagonists.

EFC13752: An open-label, randomized, parallel group study assessing the immunogenicity and safety of sarilumab administered as monotherapy in patients with active rheumatoid arthritis. The study is completed.

The primary objective was to evaluate the immunogenicity of sarilumab administered as monotherapy.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of the study is to evaluate the long term safety of sarilumab in patients with RA.

5.2 SECONDARY

The secondary objective of the study is to evaluate the long term efficacy of sarilumab in patients with RA.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is a multicenter, multinational open label long term study, for patients with RA who participated and completed EFC11072, ACT11575, EFC10832, SFY13370, EFC13752 studies or for patients from 12 weeks onward with per protocol defined lack of efficacy from EFC10832. Patients, who were randomized in Part B of the study EFC11072 in a treatment arm subsequently not retained following pivotal dose selection, were also eligible for enrollment.

Initially in LTS11210, patients received 150 mg of sarilumab SC weekly as the highest dose studied in EFC11072 Part A. The reduced dose (due to neutropenia, thrombocytopenia, or an increase in liver enzymes (ALT)), was 150 mg q2w. Once the dose regimens were selected for the Phase 3 studies (150 mg q2w and 200 mg q2w), patients already ongoing in the study at the highest dose were switched to the new highest sarilumab dose 200 mg q2w, as soon as permitted by administrative process. Patients previously assigned to the reduced dose of 150 mg q2w because of a safety issue continued to receive 150 mg q2w.

6.2 DURATION OF STUDY PARTICIPATION

The IMP will be administered for 264 weeks from the first IMP administration in LTS11210. In addition the patients will continue to be treated beyond 264 weeks until sarilumab is commercially available in their country or until 2020 at the latest when the study will be closed. (*In the UK the duration of treatment will be 264 weeks from the first study drug administration in LTS11210)*.

The total maximum duration of study participation for a patient may be up to 523 weeks.

- 1-week screening period if applicable
- 516-week maximum treatment period in LTS11210 (for the earliest patients enrolled in LTS11210 in 2010 if sarilumab is not commercialized by 2020)
- 6-week follow up period as required per protocol

Further explanation is given below and in Section 12.1.

Patients will either enter a 1-week screening period (patients from EFC11072 Part A or Part B1 and ACT11575), or enrol directly into the treatment period (for patients from EFC11072 Part B2, EFC10832, SFY13370, or EFC13752 the EOT visit in the initial study corresponds to the randomization visit in the LTS11210 study).

The duration of the treatment period in the study will be at least 264 weeks, or up to a maximum of 516 weeks (*except in the UK where the duration of treatment will be 264 weeks*).

Patients will return for the safety follow-up visit 6 weeks after the EOT visit. In case of early treatment discontinuation, patients are required to complete the EOT visit and to return for the

6-week safety follow-up visit as well. In patients who complete sarilumab treatment per protocol in countries where sarilumab is commercially available the post treatment follow-up visit may be cancelled if the patient initiates treatment with commercial sarilumab during the post treatment follow-up period. However, in this case, a telephone contact must be established with the patient to capture all AEs occurring up to the 1st administration of commercial sarilumab.

The study will be considered completed for a patient at the time he/she completes all the scheduled procedures as described in Section 12.1.

6.3 OPTIONAL PFS-S SUB-STUDY

An optional 12-week sub-study aiming to evaluate the usability of pre-filled syringe with safety system (PFS-S) will be conducted in some countries. Patients enrolled in LTS11210 at selected sites in those countries may participate in the PFS-S sub-study from Week 24 of the main study after providing written informed consent for the sub-study. However, patients may continue to participate in the main trial without participating in the PFS-S sub-study if they wish. Full details of the PFS-S sub-study are presented in Appendix R.

6.4 STUDY COMMITTEES

6.4.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) is in place for the sarilumab clinical study program. The sarilumab DMC monitors the safety of the patients participating in all ongoing sarilumab studies. The DMC is responsible for giving appropriate recommendations to the Sponsor on safety aspects during the conduct of the study, if needed. In addition to the review of serious adverse events with fatal outcome and specific adverse events, the DMC has access to complementary safety parameters (eg, vital signs, laboratory test results etc.) and access to limited efficacy data. The DMC responsibilities and the data review processes are fully described in the sarilumab DMC charter.

Members of the DMC will be independent of those performing the study, being neither investigators nor employees of the Sponsor; and without conflict of interest regarding study outcome (whatever they are).

6.4.2 Cardiovascular Adjudication Committee

An independent Cardiovascular Adjudication Committee (CAC) has been established for the sarilumab clinical study program. The role of the CAC is to apply uniform criteria for the evaluation of cardiovascular events (including retrospective events), and to adjudicate these events in a consistent and unbiased manner throughout the course of the study. The goal of the CAC is to ensure that cardiovascular events reported by the site are judged uniformly, using the same criteria by a group of experts in cardiology and neurology, independent from Sanofi. The CAC will be blinded to treatment allocation. The CAC responsibilities, detailed definitions of

cardiovascular events to be adjudicated and the adjudication processes are fully described in the CAC Charter and/or Manual of Operations.

7 SELECTION OF PATIENTS

7.1 NUMBER OF PATIENTS PLANNED

Approximately 2000 male and female patients with RA are planned to be included.

7.2 INCLUSION CRITERIA

I 01. Patients with RA who were randomized:

- in the study EFC11072 (a randomized, double-blind, placebo-controlled study in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy)
  - and who have completed Part A (12 weeks) or Part B (52 weeks) of the study EFC11072.
  - or patients randomized in Part B of EFC11072 to a treatment arm subsequently not retained following pivotal dose selection.
- in the study ACT11575 and completed the treatment period.
- in the study EFC10832:
  - and completed the 24-week study treatment period.
  - or patients from 12 weeks onward with per protocol defined lack of efficacy
- in the study SFY13370 and completed the treatment period.
- in the study EFC13752 and completed the treatment period.

I 02. Patients must give informed consent for participating in the study LTS11210 prior to any procedure related to the study.

7.3 EXCLUSION CRITERIA

Exclusion criteria related to the mandatory background therapies

E 01. Patients not willing to continue to take folic/folinic acid 5 mg weekly or greater (based on local recommendations) when using MTX.

E 02. Deleted

E 10. Patients rolling over from ACT11575, EFC11072, EFC10832, SFY13370 studies unwilling to continue the same background DMARD therapy as received in the initial study. Patients rolling over from EFC13752 study unwilling to continue sarilumab treatment without any background DMARD therapy.

E 12. Treatment with any DMARD other than those allowed per protocol (see Section 8.8) and limited to the maximum specified dosage.

Exclusion criteria related to the Sanofi compound:

E 03. Any patient who experienced an adverse event leading to permanent discontinuation from a prior study.

E 04. Deleted

E 05. Deleted

E 06. Pregnant or breast-feeding women.

E 07. Women of childbearing potential (WOCBP) 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), and/or who are unwilling or unable to be tested for pregnancy.

(For UK patients: Women of childbearing potential, unwilling to utilize adequate contraception methods or not become pregnant during the full course of the study. Adequate contraceptive measures include:

- *Placement of an intrauterine device (IUD) or intrauterine system (IUS).*

Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.

- *Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).*
- *True abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].)*

E 08. Deleted

E 09. Deleted

E 11. Patients with an abnormality(ies) or adverse event(s) that per investigator judgment would adversely affect patient´s safety and/or participation of the patient in the study.

E 13. Patients with temporary IMP discontinuation lasting > 31 days at the time of the planned first dose in the LTS11210 study.

E 14. Patients fulfilling the protocol-defined criteria for the permanent treatment discontinuation.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

- Pharmaceutical form: the pharmaceutical form of sarilumab has been modified since the initial version of the study protocol. Sarilumab, in vials (formulation C1F2), was dispensed to all patients enrolled into the study prior to the phase 3 dose selection decision. Thereafter, drug product in vials has been phased out of the study, and patients have been dispensed with drug product in prefilled syringes (pivotal formulation C2F3) once sufficient quantities were available and appropriate local approvals obtained. For completeness, all IMP formats used during the study are presented here:
  - Currently dispensed IMP for all patients:
    - Sarilumab in prefilled syringe (PFS): Glass syringes with a 27 gauge thin wall, 1/2-inch staked needle, with FM30 needle tip cap (latex free) filled at 1.14 mL with C2F3 drug product at 131.6 mg/mL (150mg dose) or 175 mg/mL (200mg dose). PFS with FM30 needle tip is the only pharmaceutical form dispensed to patients from EFC10832, SFY13370, and EFC13752.
      - Sarilumab in prefilled syringe with safety system (PFS-S) with exactly the same formulation as the PFS with FM30 needle tip cap described above. The PFS-S is used for patients in the sub-study only. Refer to Appendix R for further details of the safety system.
  - Previously dispensed IMP:
    - Sarilumab in amber glass vials: filled to 2 mL with 75 mg/mL (150mg dose), or 100 mg/mL (200mg dose) of C1F2 drug product
    - Sarilumab in PFS: Glass syringes as described above, but with FM27 rubber needle shield (needle cap may contain dry natural rubber latex)

  To ensure that the administration of the investigational product with PFS will minimally deliver the targeted doses of 150 mg and 200 mg, the PFS will contain an 8% average overfill.
- Dose per administration

  Before the phase 3 pivotal dose regimens were selected:

  - 150 mg administered weekly or every other week (reduced dose)

  After the phase 3 pivotal dose regimens were selected:

  - 200 mg administered every other week or 150 mg administered every other week (reduced dose).
- Route and method of administration: Subcutaneously in abdomen, thigh or upper arm.

Each drug administration requires one single injection. It is preferred that subcutaneous injection sites be rotated between the four quadrants of the abdomen (except the navel or waist area) or the thigh (front and side). If needed, SC injection can be administered by a caregiver in the upper arm (lateral side).

Subjects and/or their non-professional caregivers will be trained to prepare and administer study drug at the start of the double blind-treatment period of the previous study. This training must be documented in the subject's study file. The study staff should review the subject's self-administration technique at Visit 2 or V1/V2 (Week 0) for the LTS11210 study. For doses not given at the study site, diaries will be provided to record information pertaining to those injections. If the subject is unable or unwilling to administer study drug, arrangements must be made for a qualified site personnel or a caregiver to administer study drug doses that are not scheduled to be given at the study site.

The IMP administration should be taken strictly every 14 days as per protocol IMP administration schedule, however an IMP administration time window of ±3 days is permitted in exceptional circumstances (eg, the result of a repeat CBC test is not available, or an ongoing adverse event). For the subsequent IMP administration the initial IMP administration schedule should be followed again.

Note: an interval of at least 11 days between 2 IMP doses must be maintained.

8.2 NON INVESTIGATIONAL PRODUCTS

For patients rolling over from EFC11072, ACT11575, EFC10832, and SFY13370:

All patients should continue to receive the non-biologic DMARD(s) background therapy that they were receiving in the initial study until the end of study treatment. However, at any time the DMARD(s) dose can be reduced, temporarily or permanently discontinued, or a patient may switch to alternate approved non-biologic DMARD for safety or tolerability reasons. If the new DMARD is initiated the dosing as well as safety monitoring should follow the applicable local labeling information.

Each non-biologic DMARD will be recorded throughout the study on the e-CRF. Any change should be recorded on the e-CRF. DMARD(s) will not be dispensed or supplied by the Sponsor as an investigational product.

All patients receiving MTX as their background DMARD will also receive folic/folinic acid (5 mg weekly or greater) according to local guidelines in the country where the study is conducted.

For patients rolling over from EFC13752:

Treatment with non-biologic DMARDs is not allowed. All patients should continue with sarilumab monotherapy until the end of study treatment. The IMP should be permanently discontinued if any DMARD is initiated.

8.3 DELETED

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

This is an open-label study and every patient will receive sarilumab. Treatment kit numbers will be allocated via interactive voice/web response system (IVRS/IWRS). Patients will keep the same identification number that they were allocated in the previous study.

8.5 PACKAGING AND LABELING

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

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

Each IMP unit will be labeled in accordance with the local regulatory requirement.

8.6 STORAGE CONDITIONS AND SHELF LIFE

All investigational drug supplies must be kept refrigerated in appropriate, secure area (for example, a locked cabinet or a locked room) under the responsibility of the Investigator or other authorized individual and must be stored separately from other medication and in the original carton as per specification mentioned on the label.

8.7 RESPONSIBILITIES

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense 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 the applicable regulatory requirements.

All IMP shall 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) should 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 IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, 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 Access to the randomization code during the study

This section is not applicable for the study.

However, in the case of a medically urgent situation, and if the Investigator (first contact person) cannot be reached, a competent medical professional can call a 24-hour emergency number provided by the Sponsor in order to get further information on the study or for medical questions.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient at the same time as any IMP(s). All medication taken during the study should be recorded on the corresponding pages of the e-CRF including any change in dose.

8.8.1 Prohibited concomitant medication

- Use of any biologic treatment for RA is not authorized during the study until 6 weeks following the EOT visit. If any of these treatments are used, the study treatment should be permanently discontinued.
- Treatment with non-biologic DMARD(s) (such as cyclosporine, sulfasalazine, hydroxychloroquine, or cyclophosphamide) other than the DMARD(s) received in the initial study (ie, study immediately preceding LTS11210 enrollment) is not permitted until the end of treatment unless a change to an alternate approved non-biologic DMARD is made for safety or tolerability reasons. If the new DMARD is initiated the dosing as well as safety monitoring should follow local labeling information. For EFC13752 patients, the treatment with non-biologic DMARD(s) is not authorized until the end of the treatment. See Section 8.2 for additional details.
- Treatment with tofacitinib or any other JAK inhibitor is not authorized during the course of the study. If any of these treatments are used, the patient should be discontinued.
- Administration of any live (attenuated) vaccine is contraindicated (see list in Appendix K) until 3 months following the last study drug administration.
- Treatment with any investigational medicinal product other than sarilumab is not permitted.

8.8.2 Permitted concomitant medication

- Steroids
  - Oral corticosteroids are permitted to be taken at the time of study entry at the dose of ≤ 10 mg prednisone or equivalent.
  - Intranasal or inhaled corticosteroids are authorized as needed throughout the study.
  - At any time the corticosteroid dose can be modified, temporarily or permanently discontinued, or a new steroid initiated (irrespective of the mode of administration), for any reason per investigator judgment including but not limited to worsening of RA, treatment of AEs or for the prevention of corticosteroid associated side effects.
- Nonsteroidal anti-inflammatory drugs and analgesics:
  - Non-steroidal inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 inhibitors (COX-2) are permitted as needed throughout the study. The dose used should be in accordance with the approved dose in the country in which the study is conducted.
  - Narcotic or non-narcotic analgesics (with no anti-inflammatory properties) for RA pain relief are permitted based on investigator judgment that there is insufficient RA pain relief with stable maintenance NSAIDs. As limited treatment for inter-current pain, all analgesics (with no anti-inflammatory properties) are allowed. These analgesics, including acetaminophen, should be avoided within 6 hours of efficacy assessments, including physical function and quality of life assessments.
  - Acetaminophen use should be limited to 4g/24h. Specific attention should be paid to co-administration of hepatotoxic drugs (see specific Section 10.2.4).
- Cytochrome P450 enzyme substrates

  IL6 has been shown to reduce CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzyme expression in in-vitro studies. Therefore, when IL-6 is blocked using sarilumab IL-6 levels "normalize" and CYP450 enzymes may increase which could result in dose adjustment for drugs that are metabolized by CYP450 enzymes. As a precautionary measure, drugs which are metabolized via these cytochromes and with a narrow therapeutic index should be adjusted if needed: dose to be increased to maintain efficacy after initiation of sarilumab and to be decreased after sarilumab is stopped. Some examples of CYP450 substrates with a narrow therapeutic index, requiring monitoring of effect are warfarin or monitoring of drug concentration include cyclosporine, theophylline, digoxin, antiepileptics, such as carbamazepine (Carbatrol®, Tegretol®), divalproex (Depakote®), phenytoin (Dilantin®), or valproic acid (Depakene®); or antiarrhythmics, such as disopyramide (Norpace®), procainamide (Procan®, Pronestyl®), or quinidine (Quinidex®, Quin-Release Quin-G®).
- Lipid lowering drugs:

  Lipid lowering drugs are permitted. Anti-IL-6 drugs, including sarilumab are known to increase serum cholesterol levels and this effect will be closely monitored during the study. If, during the study, patients are found to have significant increase in cholesterol levels, then cholesterol lowering therapy per National Cholesterol Education program

(NCEP)Adult Treatment Panel (ATP)3 (NCEP/ATP3) or local guidelines should be initiated or the dose of concomitant lipid lowering drug(s) adjusted. A referral to a specialist should be considered when dyslipidemia is difficult to manage.

8.9 CONCOMITANT TREATMENT

A concomitant treatment is any treatment received by the patient, at the same time as the IMP(s), other than medications. Treatments received during the study should be recorded on the corresponding pages of the patient's e-CRF as appropriate.

Joint replacement is permitted during the study. The IMP should be temporarily interrupted prior to surgery as per applicable guidelines and the IMP restarted as soon as proper wound healing is established.

NOTE: The IMP can be temporarily discontinued for ≤59 days (3 IMP doses can be missed). If the re-initiation of the IMP occurs later than 38 days since the last IMP dose (2 IMP doses were already missed), the IMP has to be administered at the study site and the patient to be observed for 30 minutes for any medical events.

8.10 TREATMENT ACCOUNTABILITY AND COMPLIANCE

Measures taken to ensure and document treatment compliance and investigational medicinal product accountability include:

- Proper recording of medication treatment pack number on appropriate e-CRF page for accounting purposes.
- All medication treatment kits (containing vials, or prefilled syringes, whether empty or unused study medication) are returned by the patient at each visit.
  - As the used prefilled syringes cannot be safely returned to the study site after administration of IMP, the completed patient injection diary (returned to the site at each visit), returned treatment kit boxes and any unused prefilled syringes will be used for drug accountability purposes.
- The study coordinator tracks treatment accountability/compliance, either by diary, or by counting the number of empty IMP containers (vials or prefilled syringes), 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 investigational medicinal product administration page by comparing them with the investigational medicinal product which has been retrieved and the patient treatment log form.

8.11 RETURN AND/OR DESTRUCTION OF TREATMENTS

All partially used or unused treatments will be retrieved by the investigator. A detailed log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

Used or unused kits can be destroyed at site level upon approval of the study sponsor.

9 ASSESSMENT OF INVESTIGATIONAL PRODUCT

9.1 ENDPOINTS

9.1.1 Primary endpoint

Incidence of adverse events: (see Section 10.1)

9.1.2 Secondary endpoints

The secondary endpoints will be:

- The proportion of patients at week 12 and over time who achieve ACR20/ACR50/ACR70, DAS28 Remission, and EULAR Response.
- DAS28-CRP over time
- HAQ-DI results over time.
- Van der Heijde modified total Sharp score over time and incidence of radiographic progression of the van der Heijde modified total sharp score for the subset of patients who previously completed the study EFC11072 Part B.
- Each component of the ACR over time.
- Health economic endpoints and Patient reported outcomes: patients will continue in evaluation of the health economic endpoints as per the initial study.

9.1.2.1 ACR20/ACR50/ACR70

Signs and symptoms are assessed with a composite rating scale of the ACR (American College of Rheumatology) that includes 7 variables:

- Tender Joints Count (TJC)
- Swollen Joints Count (SJC)
- Levels of an acute phase reactant (CRP level)
- Patient's assessment of pain
- Patient's global assessment of disease activity
- Physician's global assessment of disease activity
- Patient's assessment of physical function

The details of the ACR score are presented in Appendix B.

ACR20 is defined as the percentage of patients who achieve at least 20% improvement in both tender joint count and swollen joint count and, at least 20% improvement in at least 3 of the 5 other assessments.

ACR50 is defined as the percentage of patients who achieve at least 50% improvement in both tender joint count and swollen joint count and, at least 50% improvement in at least 3 of the 5 other assessments.

ACR70 is defined as the percentage of patients who achieve at least 70% improvement in both tender joint count and swollen joint count and, at least 70% improvement in at least 3 of the 5 other assessments.

ACR scores will only be assessed up to Week 264 at the time points as per study flowchart.

9.1.2.2 DAS28-CRP

Disease activity state will be measured and presented using the disease activity score (DAS28). In this protocol, unless otherwise specified, DAS28 refers to DAS28-CRP. DAS28 is a composite score that includes 4 variables:

- Tender Joints Count (based on 28 joints - see Appendix B)
- Swollen Joints Count (based on 28 joints - see Appendix B)
- General health assessment (GH) by the patient assessed from the ACR RA core set questionnaire (patient global assessment)
- Marker of inflammation assessed by the hs-CRP.

It is a continuous measure allowing for measurement of absolute change in disease burden and percentage improvement. It has been extensively validated for its use in clinical trials and accepted by Health Authorities. The DAS28 can be calculated using the following formula:

$$\text{DAS28} = 0.56 \times \sqrt{28TJC} + 0.28 \times \sqrt{28SJC} + 0.36 \times \text{Log}(\text{CRP}+1) + 0.014 \times \text{GH} + 0.96$$

The DAS28 provides a number indicating the current activity of the RA. A DAS28 above 5.1 means high disease activity, whereas a DAS28 below 3.2 indicates low disease activity and a DAS28 below 2.6 means disease remission.

9.1.2.3 EULAR response

Improvement in disease activity will also be assessed using the EULAR response criteria:

- Good response = DAS28 improvement of >1.2 and a present DAS28 score ≤3.2
- Moderate response = DAS28 improvement of >0.6 to ≤1.2 and a present DAS28 score ≤5.1, or an improvement >1.2 and a present score >3.2
- Nonresponse = DAS28 improvement of ≤0.6, or an improvement >0.6 to ≤1.2 and a present DAS28 score >5.1

9.1.2.4 Van der Heijde modified Total Sharp Score

The van der Heijde modified Sharp method is a composite X-ray scoring system used to assess structural (joint) disease progression in RA (see Appendix C). The method evaluates both joint erosions (JE) and joint space narrowing (JSN) in bilateral hand and foot joints.

The change from baseline in van der Heijde modified total Sharp score will be evaluated for patients who completed the EFC11072 Part B study in order to demonstrate maintenance of sarilumab effect on joints. It will be assessed at week 48, 96, 144 and 192, or at the end of treatment for patients who prematurely discontinue from the study before Week 192.

NOTE: the sponsor will not perform any medical evaluation on collected X-rays. They will be blindly assessed by independent graders and modified Van Der Heijde Total Sharp Score will be calculated per patient per visit.

9.1.2.5 Physical Function

Improvement in physical function is assessed by the change from baseline (original study) in HAQ-DI at week 48, 96, 144, 192, 240, 264, and EOT, if EOT is prior to Week 264. It is based on the HAQ-DI assessment that is completed at each visit by the patient, as one of the ACR components.

The HAQ-DI is composed of 8 categories as follows: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities, for which there are at least 2 questions by category. The patient will be asked to score how difficult he/she feels it is to perform such activities using a 0 to 3 scoring (0=without any difficulty, 1=with some difficulty, 2=with much difficulty and 3=unable to do). If the patient is using assistance for any of these activities, scoring may be adjusted. For each category, the highest score given for one of the question is attributed to the category. The total score is the sum of all categories' scores divided by the number of answered categories (at least 3 categories should be answered) (see Appendix J).

9.1.2.6 ACR Components

Each component of the ACR will be analysed as other secondary outcomes over time.

All ACR components will be assessed up to Week 264.

After Week 264, TJC and SJC (both based on 28 joints), patient´s global assessment of disease activity and hs-CRP will still be assessed to calculate DAS28.

9.1.2.7 Health economic assessment and Patient reported outcomes (PROs)

- Health economic assessments and PROs will be performed up to Week 264 as defined in the initial study and as specified in the study flowchart (See section 1.2).

- The Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-Fatigue) will be used to assess fatigue. The FACIT-Fatigue is a 13-item questionnaire rated 0 to 4 originally developed to measure fatigue in patients with cancer and widely used in rheumatoid arthritis patients that demonstrates good consistency and sensitivity to change. The patient will be asked to answer 13 questions rated 0 to 4 (0 = not at all, 1 = a little bit, 2 = some what, 3 = quite a bit, 4 = very much) (see Appendix F). The patient will be asked to fill in the questionnaire at different site visits (see flow chart, Section 1.2)
- The Work Productivity and Activities Impairment (WPAI) will be assessed for patients coming from EFC11072 and ACT11575 only. The WPAI was developed by Margaret Reilly for assessing productivity losses by measuring the effect of general health and symptom severity on work as well as usual activity productivity. Specific-disease WPAI exists and can be adapted to different pathologies. The RA WPAI (Appendix G): instrument consists of 6 questions that ask the subject the number of hours missed from work (ie, absenteeism) due to RA, the number of hours missed from work for anything other than RA, the number of hours totally worked, as well as how much the RA does affect the productivity at work or the ability to do daily activities over the past 7 days. The instrument can be self-, interview-, or telephone-administered and takes less than 5 minutes to complete (~3 minutes). The 4 scores of the questionnaire are expressed as impairment percentages with higher numbers reflecting greater impairment and decreased productivity. The 4 scores are:
  1. Percent work time missed due to RA
  2. Percent impairment while working due to RA
  3. Percent overall work impairment due to RA
  4. Percent activity impairment due to RA
- The WPAI has been tested in many disease states including migraine, arthritis, hypertension, diabetes, and depression and is adaptable to specific health problems such as RA. Inclusion of this measure in the study assesses the impact of sarilumab on a major component of subjects' lives, which is their ability to perform daily activities and/or be able to work. The patient will be asked to fill in the questionnaire at different site visits (see flow chart, Section 1.2)
- Assessment of joint replacement and joint procedures if any will be performed: total joint replacement (arthroplasty).
- Sleep: Rheumatoid arthritis, like other chronic illness, is associated with sleep disturbances. Sleep disturbance is linked to pain, mood, and disease activity. The effect of sarilumab on pain will be assessed on a VAS scale (see Appendix H). The patient will be asked to fill in the questionnaire at different site visits (see flow chart, Section 1.2)
- SF-36: The Short-Form 36 (SF-36) is a generic questionnaire measuring general health status (quality of life). It is one of the most frequently used and has been extensively validated in rheumatologic disease (see Appendix I). The patient will be asked to fill in the questionnaire at different site visits (see flow chart, Section 1.2)

- The Rheumatoid Arthritis-Work Productivity Survey (WPS-RA): The WPS-RA is a validated questionnaire that evaluates productivity limitations within work and within home associated with RA over the previous month.

  It is interviewer-administered, is based on patient self-report. It contains 8 items that include 3 work productivity related items and 5 home productivities related items (household activities) (see Section 27, Appendix Q) plus 1 item related to the employment status.

  Within work

  - Number of days of work missed
  - Number of days with productivity ≤ 50% at work
  - Arthritis interference with work productivity on a scale of 0 to 10 (0 = 'no interference' and 10 = 'complete interference')

  Within the home

  - Number of days of household work missed
  - Number of days with productivity ≤ 50% in household work
  - Number of days of family, social, or leisure activities missed
  - Number of days with outside help
  - Arthritis interference with household work productivity on a scale of 0 to 10 (0 = 'no interference' and 10 = 'complete interference')

9.2 DELETED

9.3 PHARMACOKINETICS AND IMMUNOGENICITY

Pharmacokinetics and immunogenicity assessment will be performed in all patients.

9.3.1 Sampling time

Serum samples will be collected for determination of functional sarilumab, anti-sarilumab antibody (also known as anti-drug antibody (ADA)) and IL-6 according to the Study Flow Chart (Section 1.2). The date of collection should be recorded in the e-CRF.

Serum concentrations of bound (serum sarilumab-sIL-6Rα complex) and functional sarilumab were intended to be analyzed in the study. After the completion of EFC11072 Part B study, the Sponsor made the decision to only analyze functional sarilumab concentrations.

If a serious adverse event (SAE) occurs in a patient, serum samples should be collected for determination of sarilumab at or near the onset and completion of the occurrence of the event, if possible. The exact date of sample collection and last dose must be recorded on the e-CRF.

9.3.2 Pharmacokinetic handling procedure

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

An overview of sample handling procedures for pharmacokinetics (PK), anti-sarilumab antibody, and IL-6 is provided below:

Table 1 - Summary of handling procedures for sarilumab, anti-sarilumab antibody, and IL-6

	Sarilumab	Anti-sarilumab antibody	IL-6
Blood Sample Volume	6 mL	6 mL	2.5 mL
Anticoagulant	None	None	None
Blood Handling Procedures	See Operational Manual	See Operational Manual	See Operational Manual
Serum Aliquot Split	Two aliquots	Two aliquots	One aliquot
Serum Storage Conditions	< 6 month: below -70°C (preferred) / -20°C > 6 month: below -70°C	< 6 month: below -70°C (preferred) / -20ºC > 6 month: below -70°C	-20°C
Serum Shipment Condition	In dry ice	In dry ice	In dry ice

9.3.3 Bioanalytical method

Serum samples will be assayed using validated methods as described below:

Table 2 - Summary of bioanalytical methods for sarilumab and anti-sarilumab antibody

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

In addition, IL-6 will be measured using validated assays.

9.4 SERUM AND RNA BIOMARKERS

Please refer to the LTS11210 operations laboratory manual for a description of the collection, handling, storage, and shipment of the biomarker specimens.
Potential studies may include examining markers related to IL-6 signaling, response to sarilumab, or related to the disease of RA. It is anticipated that the serum and RNA biomarker samples will be stored for up to 15 years (or as appropriate, according to applicable regulations) after completion of the final report of the main clinical trial. Storage after the end of the study will be at an accredited, dedicated long term biological sample storage facility which has established a strict and comprehensive security and confidentiality system. Samples will remain the property of the Sponsor and will be used only for the purposes described here, upon request by the Sponsor.

9.4.1 Serum for future biomarker analysis

A serum sample (5 ml) will be collected for future biomarker analysis at the EOT visit of the initial study, and at Week 2, Week 12, and Week 48 (except EFC13752 patients).

9.4.2 RNA for future biomarker analysis

Whole blood samples for ribonucleic acid (RNA) expression profiling (non-genetic analysis) will be collected at Week 0 (V2 or V1/V2), prior to treatment, and at Week 2/Visit 3 site visits only (except for SFY13370 and EFC13752 patients).

If week 2/Visit 3 is scheduled as a “home visit”, the whole blood sample for RNA will not be collected.

10 PATIENT SAFETY

10.1 SAFETY PARAMETERS ASSESSED IN THIS TRIAL

- **Adverse events:** at every visit, the Investigator will ask the patient how he has felt since the last study visit.
- **Vital signs:**
  - Vital signs including temperature, blood pressure, and heart rate will be collected prior to dosing per specifications on the study flow chart (see Section 1.2):
  - Body temperature will be collected using the same method for a given patient. Any fever: body temperature ≥ 38°C should be recorded as an adverse event and the Investigator should perform all investigations necessary to rule out infection (see Section 10.2).
  - Blood pressure will be measured under standardized conditions, using the same well calibrated apparatus. Both systolic and diastolic blood pressure should be recorded. Supine or sitting blood pressure should be checked after 2 minutes of rest. Standing blood pressure is obtained 1 minute after the patient stands up. The same arm should be used to measure blood pressure throughout the study.
- **Physical examination:** A complete physical examination including a neurological examination will be performed as specified in the flowchart (see Section 1.2). Any clinically significant abnormalities should be reported in the patient e-CRF as an adverse event. Body Weight should be taken on a regular basis per specifications on the study flow chart (see Section 1.2) Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study.
- **Tuberculosis assessment:** (see Section 1.2 and Section 10.2)
- **Electrocardiogram** (ECG): A standard 12-lead ECG will be performed as specified in the flowchart (see Section 1.2). Heart rate, QRS duration, PR interval, QT interval, ST deviation, T-wave morphology, U wave presence or absence will be determined using a centralized automatic and manual reading of all ECG.
- **Laboratory safety**: Blood will be taken before study drug dosing at the study site or at home by qualified personal. The following laboratory tests will be performed per specifications on the study flow chart (see Section 1.2):
  - Hematology
    Including: Hemoglobin, hematocrit, Red Blood Cell (RBC) morphology (if blood cell count is abnormal), WBC with differential, and platelet count

- Liver Function Test
  Including: Prothrombin Time (PT), albumin, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), total bilirubin, conjugated bilirubin, unconjugated bilirubin. NOTE: after Week 264, PT will no longer be tested.

– Lipids profile **(**patients need to be fasting**)**
  Including: total cholesterol (TC), High Density Lipoprotein (HDL) cholesterol, Low Density Lipoprotein (LDL) cholesterol, triglycerides, Apolipoprotein A and Apolipoprotein B (Apolipoprotein A and B determination is not performed in SFY13370 study and results will not be available for the initial LTS11210 visit for SFY13370 patients). NOTE: after Week 264, only total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides will be tested.

- Clinical Chemistry (patients need to be fasting)
  Including: fasting glucose, total protein, calcium, sodium, potassium, Lactate Dehydrogenase (LDH), urea nitrogen and creatinine. Creatinine clearance will be calculated only at initial visit and during the study if clinical indicated.

- For women of child-bearing potential: urine pregnancy testing will be performed as per study flow chart in Section 1.2. From V6, the site will dispense urine pregnancy kits to the patients who will perform the test at home on a monthly basis. The pregnancy test should be completed prior to any X-ray procedure. If any interim urine pregnancy test performed by the patient is positive, the patient should immediately report to the investigator for appropriate follow-up and pregnancy reporting as appropriate.

- Urine analysis: including specific gravity, pH, glucose, blood, ketones, proteins, bilirubin, urobilinogen, nitrate, leukocytes will be performed per specifications on the study flow chart using a dipstick. If any parameter is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis will also be performed by central laboratory. NOTE: after Week 264, urine analysis will no longer be performed.

- ANA/Anti-ds-DNA: testing will be done per specifications on the study flow chart (see Section 1.2).

- Hepatitis B and C: serology will be determined as clinically indicated (see Section 10.2.4).

- HIV**:** testing will be done anytime during the study when the patient has been at risk for HIV infection as per investigator judgment.

  Note: Local regulations or recommendations regarding regular eg, yearly HIV testing should be followed using a central or local laboratory facility.

- Anti-sarilumab antibody: testing will performed per specifications on the study flow chart (see Section 1.2)

Note that the laboratory values from the end of treatment in the study EFC11072, ACT11575, EFC10832, SFY13370, or EFC13752 studies will be the laboratory values for the initial visit of the LTS11210 study.

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

10.2 SAFETY INSTRUCTIONS

10.2.1 Infections

Biologics including TNF-α inhibitors and tocilizumab (another IL-6 receptor inhibitor similar to sarilumab) have been associated with an increased risk of infection, including black box warnings for serious infections leading to hospitalization or death.

In the ongoing phase 3 program, serious infections including life threatening sepsis, have been reported, some notably associated with minor trauma. As a precautionary measure, investigators should carefully follow any signs of infection with particular care to identify potential infective complications in immune-suppressed individuals where superficial skin wounds or abrasions may lead to serious infections including necrotizing fasciitis and/or sepsis.

Any infection should be reported by the Investigator as an adverse event and a corresponding e-CRF form should be filled in. Treatment with antibiotics if any should be recorded with the route of administration.

- **Clinically significant infection:** Section 10.5.4 defines clinically significant infections that require pre-specified monitoring and should be reported as adverse events of pre-specified monitoring/adverse events of special interest (AEPM/AESIs) with immediate notification. In case of suspicion of clinically significant infection, a complete diagnosic work-up should be performed including but not limited to cultures for bacterial infections, fungi and/or mycobacteria, histopathological or cytological evaluation, antigen detection and serum antibody titers. The type of infection should be listed in the e-CRF form. The patient should be referred to a specialist if needed for diagnosis and treatment. In addition, the study Investigator should determine if the infection qualifies for serious adverse event reporting or not.
- Note: Systemic opportunistic infections should be reported as serious.
  - The IMP should be temporarily discontinued in case of infection requiring oral or parenteral treatment with antibacterial, antiviral and/or antifungal agents (See Section 11.1) or permanently discontinued in case of confirmed opportunistic infections including but not limited to TB. (See Section 11.2.1 and Appendix M).
- **Tuberculosis assessment*:*** Sarilumab is a biologic treatment that may induce immunosuppression, including the risk of reactivation of latent tuberculosis. A special warning of the increased risk of tuberculosis is included in the labels of TNF antagonists and tocilizumab.

  As a precautionary measure, patients at risk for tuberculosis will be permanently discontinued from the study.

  A clinical examination and history will be performed at every visit to assess any signs and symptoms of tuberculosis or contact with a patient with active tuberculosis.

A QuantiFERON TB Gold test can be performed at any time during the course of the study in case of suspicion of tuberculosis. A chest X-ray should be performed in all patients with suspected tuberculosis.

In case of suspicion of TB, the Investigator should refer the patient to a specialist for a complete examination. The study drug should be discontinued until TB is ruled out.

Repeat chest radiographs should be performed as indicated by local treatment guidelines or practice for monitoring while on immunosuppressive/immunomodulatory therapy. If such guidelines are not available/ applicable, a chest X-rays should be performed when clinically indicated.

10.2.2 Demyelinating / Neurological events

Any demyelinating event or significant, unexplained neurological symptom should be considered as an adverse event with prespecified monitoring (see Section 10.5.4). Refer to Section 11.2 for demyelinating/neurological events requiring permanent treatment discontinuation.

Rarely, biologics have been associated with Progressive Multifocal Leukoencephalopathy (PML). The investigator should check any signs that might be suggestive of a PML at every visit: such as, but not limited to, unusual weakness, loss of coordination, changes in vision, difficulty speaking and sometimes personality changes. In case of suspicion of an event potentially related to a demyelinating event or significant, unexplained neurological symptom during the course of the study, the patient should be referred to a neurologist for a complete examination.

10.2.3 Autoimmunity and Lupus-like syndrome

Anti DNA antibodies: ANA (Antinuclear antibody) and Anti- double- stranded DNA (Anti- ds-DNA) antibody will be performed to assess the effect of sarilumab to induce autoimmune disorders most specifically for Systemic Lupus Erythematosus (SLE). Indeed, immunosuppressant agents such as TNF antagonists have been associated with induction of SLE and SLE like syndromes. Anti-ds DNA antibody will be tested only if ANA is positive (≥1:160 titer).

The presence of either of these antibodies may be without clinical consequence or associated with a clinical syndrome. Their significance will be determined on a by-patient basis.

If a diagnosis of lupus-like syndrome is suspected, this should be reported as an AEPM/AESI (see Section 10.5.4).

10.2.4 Liver Function

Transient, generally mild, elevation of transaminases has been observed with sarilumab. See the Clinical Investigator's Brochure (CIB).

Moreover, the co-administration of MTX or NSAID may represent an additional risk factor for observing signs of hepatotoxicity which is reflected in the American College of Rheumatology

(ACR) guidelines (12). The investigator is recommended to monitor transaminases in any patient receiving MTX but without any defined threshold for transaminases to start reducing MTX dosage which is thus left to the investigator judgement.

Please refer to Section 10.5.4 for LFT abnormalities to be reported as AEPM/AESI with or without immediate notification.

The Sponsor relies on the Investigator´s judgement for adapting concomitant medication, including dose reduction of MTX dosage, in case of LFT abnormalities within the guidelines below.

In the present protocol, in order to closely follow LFTs, assessment of ALT, AST, alkaline phosphatase, prothrombin time, albumin, total bilirubin, conjugated bilirubin and unconjugated bilirubin will be performed per specifications on the study flow chart (see Section 1.2).

- The study drug should be permanently discontinued in case of confirmed ALT > 5 ULN or in case of confirmed ALT>3 ULN and concomitant total bilirubin >2 ULN (unless the patient has a documented Gilbert's disease). A complete serological and ultrasonography work-up should be conducted in case of ALT >5 ULN or ALT>3 ULN and concomitant bilirubin >2 ULN (see Appendix L).
- If ALT ≥3 ULN and ≤5 ULN and bilirubin ≤2 ULN, administration of study drug must be temporarily interrupted, and the study Investigator should immediately contact the patient to arrange for repeat LFTs within 48 hours from the Investigator's awareness of the abnormal LFT results:
  - IMP should be temporarily interrupted until the ALT is below <3 ULN then restarted **at the dose of 150 mg q2w** at the Investigator´s discretion.
  - LFTs should be repeated according to the provided guideline and at a minimum of every 7 days until conditions for resumption of IMP administration are met (see Appendix L).

10.2.5 Neutrophils

Refer to Section 10.5.4 criteria for reporting neutropenia as AEPM/AESI with or without immediate notification.

For all patients, a CBC test must be performed a few days before or at Visit 3, but not earlier than the 12th day after the first dose of IMP administration (using either designated central lab or local laboratory facility), and results reviewed prior to the administration of the 2nd dose of study drug in order to confirm that the neutrophil count is not within the protocol-defined limits for temporary, or permanent discontinuation of study drug.

For all subsequent visits, in order to prevent the administration of study drug in patients at risk for severe neutropenia, whenever the neutrophil count is ≥ 1000/mm^3 but less than the lower limit of normal (LLN) based on designated central laboratory test specifications, the CBC test (with differential) must be **repeated** to confirm that the neutrophil count is not within the protocol-

defined limits for temporary, or permanent discontinuation of study drug, before the next administration of study drug. The outlined procedures below will be followed:

- Contact patient as soon as possible and schedule "repeat CBC blood test"; the repeat blood test can be arranged using the designated central lab or a local laboratory facility.
- If the results of the "repeat CBC blood test" (either designated central lab or local laboratory facility results) confirm that the neutrophil count is ≥ 1000/mm^3 (1.0 GI/L), the study drug may be administered.
- If the results of the "repeat CBC blood test" (either designated central lab or local laboratory facility results) demonstrate that the neutrophil count is < 1000/mm^3 (1.0 GI/L), the study drug must be temporarily or permanently discontinued, per protocol stopping rules defined below, and in Appendix L.
- Note: All per protocol-scheduled CBC tests must be performed using the designated central lab, even in circumstances when a local laboratory facility is also used to determine the neutrophil count before dosing.

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

- Study drug must be temporarily discontinued; the patient must be assessed for evidence of infection and CBC blood test repeated within 48 hours from the study Investigator's awareness of neutrophil count ≥ 500/mm^3 and <1000/mm^3.
- Discontinuation of study drug is maintained until the neutrophil count returns to ≥ 1000/mm^3 (Appendix L).
- After the patient meets all requirements for resumption of study drug administration, including neutrophil count ≥ 1000/mm^3, then study drug administration may resume **at the dose of 150 mg q2w**.

In case of a decrease in neutrophil count < 500/mm^3 or if neutrophil count < 1000/mm^3 and signs of infection:

- Study drug must be permanently discontinued.
- The patient must be assessed for evidence of infection and CBC blood test repeated within 48 hours from the study Investigator's awareness of neutrophil count < 500/mm^3, or < 1000/mm^3 and signs of infection.
- It is recommended to admit the patient to the hospital in case of neutrophil count < 1000/mm^3 with suspicion of infection.
- Neutrophil count <500/mm^3 persisting for at least 5 days is to be reported as a serious adverse event.

10.2.6 Platelets

Refer to Section 10.5.4 criteria for reporting thrombocytopenia as AEPM/AESI with or without immediate notification.

For all patients, a CBC test must be performed a few days before or at Visit 3, but not earlier than the 12th day after the first dose of IMP administration (using either designated central lab or local laboratory facility), and results reviewed prior to the administration of the 2nd dose of study drug in order to confirm that the platelet count is not within the protocol-defined limits for temporary, or permanent discontinuation of study drug.

For all subsequent visits, in order to prevent the administration of study drug in patients at risk for thrombocytopenia, whenever the platelet count is below the LLN based on designated central laboratory test specifications, the CBC test must be **repeated** to confirm that the platelet count is not within the protocol-defined limits for temporary, or permanent discontinuation of study drug, before the next administration of study drug. The outlined procedures below will be followed:

- Contact patient as soon as possible and schedule "repeat CBC blood test"; the repeat blood test can be arranged using designated central lab or a local laboratory facility.
- If the results of the "repeat CBC blood test" (either designated central lab or local laboratory facility results) confirm that the platelet count is ≥ 100,000/mm^3 (100 GI/L), the study drug may be administered.
- If the results of the "repeat CBC blood test" (either designated central lab or local laboratory facility results) demonstrate that the platelet count is below 100,000/mm^3 (100 GI/L), the study drug must be temporarily or permanently discontinued, per protocol stopping rules defined below, and in Appendix L.
- Note: All per protocol-scheduled CBC tests must be performed using designated central lab, even in circumstances when a local laboratory facility is also used to determine the platelet count before dosing.

In case of a decrease in platelet count to a level ≥ 50,000/mm^3 and < 100,000/mm^3:

- Study drug must be temporarily discontinued; the patient must be assessed for evidence of spontaneous bleeding, and CBC blood test repeated within 48 hours from the study Investigator's awareness of platelet count ≥ 50,000/mm^3 and < 100,000/mm^3.
- Discontinuation of study drug is maintained until the platelet count returns to ≥100,000/mm^3 (see Appendix L).
- After the patient meets all requirements for resumption of study drug administration, including platelet count ≥100,000/mm^3, then study drug administration may resume **at the dose of 150 mg q2w**.

The study drug must be permanently discontinued if platelet count is <50,000/mm3 or if <100,000/mm^3 with spontaneous bleeding (see Appendix L).

10.2.7 Systemic Hypersensitivity reactions / Anaphylaxis

Severe, systemic hypersensitivity reactions (in rare cases fatal anaphylaxis), have been reported to occur following exposure to biological drugs, including tocilizumab. Infrequent, mild to moderate, systemic hypersensitivity reactions have been observed with sarilumab.

Patient at study site visits should be monitored for 30 min after the injection. Patients that self-administer IMP should be aware of the clinical signs and symptoms of allergic reactions, and limit strenuous activity for 30 minutes after self-injection. Any problem should be documented in the patient's diary or medical notes. In case of systemic hypersensitivity reaction, including anaphylaxis (see Appendix O for the clinical criteria for diagnosing anaphylaxis), the study drug should be permanently discontinued and the study Investigator should determine if the event qualifies for serious adverse event reporting (see Section 10.4 and Section 10.5.2). If the clinical criteria for diagnosing anaphylaxis are met per Appendix O, then appropriate treatment should be administered immediately and the adverse event must be reported as an SAE and AEPM/AESI with immediate notification.

10.2.8 Diverticulitis and Gastrointestinal perforation

Gastrointestinal perforations have been reported as complications in patients with diverticulitis who have been treated with tocilizumab.

Gastro-intestinal perforation is an AESI with immediate notification to be reported as SAE. Confirmed diverticulitis or gastrointestinal ulceration should be reported as AESI without immediate notification (see Section 10.5.4).

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

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

10.2.9 Acute renal failure

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

10.2.10 Management of dyslipidaemia, cardiovascular events, and deaths

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

As rheumatoid arthritis is a known independent risk factor for cardiovascular events, 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 (ATP) III or applicable local guideline (http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf).

Specific cardiovascular events, as listed in Section 10.5.4, and all deaths will be reported as AESI with immediate notification and should always be reported as serious adverse events. These events will be subject to an adjudication process via the Cardiovascular Adjudication Committee described in Section 6.4.2.

10.3 ADVERSE EVENTS MONITORING

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

10.4 DEFINITIONS OF ADVERSE EVENT (AE) AND SERIOUS ADVERSE EVENT (SAE)

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

An **Adverse Event of Special Interest** also known as an **Adverse Event of Pre-specified Monitoring** (AEPM/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 rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. The AESI/AEPMs may be added or removed during a study by protocol amendment.

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 intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following medical important events intend to serve as a guideline for determining which condition has to be considered as a medically important event. It 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…),
  - convulsions (seizures, epilepsy, epileptic fit, absence…).
- Development of drug dependency or drug abuse.
- ALT >3 ULN + total bilirubin >2 ULN or asymptomatic ALT increase >10 ULN.
- Neutrophil count <500/mm^3 lasting for at least 5 consecutive days
- Suicide attempt or any event suggestive of suicidality.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Bullous cutaneous eruptions.
- Cancers diagnosed during the study or aggravated during the study.
- Chronic neurodegenerative diseases, newly diagnosed or aggravated during the study.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 Adverse Events

All AEs regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form, until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) included in the CRF.

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 the NIMP (not assessed in EFC13752 patients).

The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal (or baseline), 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 Sponsor.

- Patients who experience an ongoing SAE or an AESI with immediate notification, at the pre-specified study end-date, should be followed until resolution, stabilization, or death and related data will be collected.

When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.

Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if they are medically relevant: symptomatic or requiring either corrective treatment or consultation or leading to discontinuation or modification of dosing and/or fulfilling a seriousness criterion and/or is defined as an AE with pre-specified monitoring (AEPM/AESI).

10.5.2 Serious Adverse Events

In the case of a serious adverse event the Investigator must immediately:

- ENTER (within 24 hours of knowledge) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send the notification to the Monitoring Team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) the 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 source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for Lab data, concomitant Medication, patient status.) should be sent (by fax or e-mail) to the Monitoring Team within 24 hours of knowledge. In addition, any effort should be made to further document each Serious AE that is fatal or life threatening within the week (7 days) following initial notification.
- A back-up plan is used (using paper flow) when the e-CRF system does not work.
- In case of 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, this should be reported to the Monitoring team.

10.5.3 Deleted

10.5.4 Adverse events of special interest/Adverse events with pre-specified monitoring (AESI/AEPM)

The needs for specific monitoring, documentation, and management of AEPM/AESIs are described in this section.

The decision to report AEPM/AESI as a SAE is the same as for any adverse event; if the event meets any seriousness criteria as per the Investigator’s judgment, it should be reported as an SAE. If the AEPM (just as any other adverse event) does not meet seriousness criteria as per the Investigator’s judgment, it should be reported as a nonserious event. Certain AEPM/AESI will require immediate notification to the Sponsor, even if not fulfilling seriousness criteria, while others will not.

For the following AEPM/AESI, the Sponsor will be informed immediately (i.e., within 24 hours of knowledge), even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the e-CRF, following the same process as described for the SAEs.

- Clinically significant infections including:
  - Confirmed diagnosis of opportunistic infection based on the investigator's assessment following appropriate diagnostic workups and consultations.

    Note: For reporting purposes, any infection from the list of potential opportunistic infections provided in Appendix M should be reported as AESI with immediate notification, even it is not considered to be an opportunistic infection based on the investigator's assessment.
  - Tuberculosis or initiation of medication for suspected tuberculosis
  - Parasitic and fungal infections not considered opportunistic infections (Note: for fungal infections only systemic and/or extensive cutaneous cases)
  - Infection requiring prolonged medication (>14 days). These are infections which require treatment (continuous or intermittent) for > 14 days, with antibiotics, antifungals, or antivirals (exclude when medications are only administered topically).
  - Infections requiring any parenteral antibiotics, parenteral antifungals, or parenteral antiviral agents
- Anaphylaxis (see Section 10.2.7)
- Increased alanine aminotransferase (see Section 10.2.4 and Appendix L): ALT increase leading to permanent discontinuation
- Neutropenia (see Section 10.2.5 and Appendix L): Grade 4 or any neutropenia leading to permanent discontinuation
- Thrombocytopenia (see Section 10.2.6 and Appendix L) leading to permanent discontinuation
- Lupus like syndrome
- Demyelinating events (including suspicion of PML) or significant unexplained neurological symptoms meeting seriousness criteria
- Gastrointestinal perforation
- Specific cardiovascular events and deaths (see Section 10.2.10):
  - Myocardial infarction
  - Stroke
  - Hospitalization due to unstable angina
  - Hospitalization due to heart failure
  - Hospitalization due to transient ischemic attack
  - Deaths (cardiovascular and noncardiovascular)

- Pregnancy:
  - Pregnancy occurring in a female patient included in the clinical study (as well as pregnancy occurring in a female partner of a male patient included in the study with IMP/NIMP) will be recorded as a pre-specified AE with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria.
  - In the event of pregnancy in a female patient included in the trial, IMP should be discontinued.
  - The follow-up of the pregnancy in a female participant or in a female partner of a male participant will be mandatory until the outcome has been determined.
- Symptomatic Overdose with IMP/NIMP:
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the dose of IMP during an interval of less than 11 days (NOTE: this definition was less than 6 days for patients on the initial weekly dosing regimen in the study). The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.
  - An overdose (accidental or intentional) with any NIMP (as defined in Section 8.2) is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice ~~of~~ the intended dose within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate adverse event forms.

In addition, the following AESIs/AEPMs with immediate reporting must always be considered as medically important if not fulfilling any other seriousness criteria (see Section 10.4) and reported as serious adverse events.

- Systemic opportunistic infections
- Grade 4 neutropenia lasting for at least 5 days
- Anaphylaxis fulfilling the criteria in Appendix O
- Demyelinating events (including suspicion of PML), or significant, unexplained neurological symptoms meeting seriousness criteria
- Gastrointestinal perforation
- Myocardial infarction
- Stroke
- Hospitalization due to unstable angina
- Hospitalization due to heart failure
- Hospitalization due to transient ischemic attack
- Deaths (cardiovascular and noncardiovascular)

For the following AEPM/AESI, the Sponsor **will not** require immediate notification; however if the event meets any seriousness criteria as per the Investigator's judgment, it should be reported as a SAE.

- Neutropenia grade 3 (<1000 and ≥500/mm^3) without permanent treatment discontinuation (see Section 10.2.5)
- Thrombocytopenia (<100 000/mm^3) without permanent treatment discontinuation (see Section 10.2.6)
- ALT elevation ≥3 x ULN without permanent treatment discontinuation (see Section 10.2.4)
- Confirmed diverticulitis or gastrointestinal ulceration (see Section 10.2.8)
- Significant unexplained neurological symptoms not meeting seriousness criteria (see Section 10.2.2)
- Asymptomatic overdose (definition described above) with IMP/NIMP. The circumstances (ie, accidental or intentional) and the lack of symptoms (ie, asymptomatic) should be clearly specified in the verbatim.

Table 3 - 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	Routine	Any AE that is not SAE or AEPM/AESI Any laboratory, vital sign, or ECG abnormality (non-SAE) other than those specifically listed in another section that is: symptomatic, requiring corrective treatment or consultation, leading to IMP discontinuation or dose modification	Yes	No	No
All Serious Adverse Events	Expedited (within 24 hours of knowledge)	Any AE/AEPM/AESI meeting seriousness criterion per Section 10.4	Yes	Yes	As needed for selected AESI
AESI **WITH** immediate notification	Expedited (within 24 hours of knowledge)	Clinically significant infections including: Confirmed diagnosis of opportunistic infection based on the investigator's assessment following appropriate diagnostic workups and consultations. Note: For reporting purposes, any infection from the list of potential opportunistic infections provided in Appendix M should be reported as AESI with immediate notification, even it is not considered to be an opportunistic infection based on the investigator's assessment. Infection requiring prolonged medication (>14 days). These are infections which require treatment (continuous or intermittent) for > 14 days, with antibiotics, antifungals, or antivirals (exclude when medications are only administered topically). Infections requiring any parenteral antibiotics, parenteral antifungals, or parenteral antiviral agents Tuberculosis or initiation of medication for suspected tuberculosis Parasitic and fungal infections not considered opportunistic infections (Note: for fungal infections only systemic and/or extensive cutaneous cases)	Yes	Yes	Yes
		ALT increase leading to permanent discontinuation	Yes	Yes	Yes
		Grade 4 neutropenia or any neutropenia leading to permanent discontinuation	Yes	Yes	No
		Thrombocytopenia leading to permanent discontinuation	Yes	Yes	No
		Lupus like syndrome	Yes	Yes	No

EVENT CATEGORY	REPORTING TIMEFRAME	SPECIFIC EVENTS IN THIS CATEGORY	CASE REPORT FORM COMPLETION		
			AE form	Safety complementary form	Other specific forms
		Pregnancy of a female patient/or female partner of male patient	Yes	Yes	Yes[a]
		Symptomatic overdose with IMP/NIMP	Yes	Yes	No
		In addition, AESI **WITH** immediate notification to **always be reported as serious:**			
		• Systemic opportunistic infection	Yes	Yes	Yes
		• Grade 4 neutropenia lasting for at least 5 days	Yes	Yes	No
		• Anaphylaxis (defined in Appendix O, report as SAE)	Yes	Yes	No
		• Gastrointestinal perforation	Yes	Yes	Yes
		• Demyelinating events (including suspicion of PML) or significant, unexplained neurological symptoms meeting seriousness criteria	Yes	Yes	Yes
		• Specific cardiovascular events and deaths: - Myocardial infarction - Stroke - Hospitalization due to unstable angina - Hospitalization due to heart failure - Hospitalization due to transient ischemic attack - Deaths (cardiovascular and noncardiovascular)	Yes	Yes	No[b]
AESI **WITHOUT** immediate notification (non-SAE)	Routine	Neutropenia grade 3 (<1000 and ≥500 mm^3) without permanent treatment discontinuation	Yes	No	No
		Thrombocytopenia (<100,000/mm^3) without permanent treatment discontinuation	Yes	No	No
		ALT elevation ≥ 3 x ULN without permanent treatment discontinuation	Yes	No	Yes
		Confirmed diverticulitis or gastrointestinal ulceration	Yes	No	Yes
		Demyelinating events or significant, unexplained neurological symptoms not meeting seriousness criteria	Yes	No	Yes
		Asymptomatic overdose with IMP/NIMP	Yes	No	No

- Reminder: Safety Complementary Forms should be completed for all SAEs, AESIs with immediate notification, pregnancies, and symptomatic overdoses

a This corresponds to "Drug exposure via parent data collection form" used by Global Pharmacovigilance and Epidemiology.

b No specific form in CRF but a cardiovascular adjudication package needs to be submitted to the Cardiovascular adjudication committee.

10.6 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the IMP Suspected Unexpected Serious Adverse Reaction (SUSAR), to the Health Authorities, IECs/IRBs as appropriate and to the Investigators.

In addition, the Sponsor will report in an expedited manner all SAEs that are expected and at least reasonably related to the IMPs to the Authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected: eg, arthralgia related to RA.

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered as unexpected.

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

11 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 if the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

11.1 TEMPORARY TREATMENT DISCONTINUATION WITH INVESTIGATIONAL PRODUCT(S)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs eg, suspected malignancy or because of abnormal laboratory values.

The following is a list of criteria for temporary discontinuation. This list is not exhaustive and IMP may be temporarily discontinued for additional reasons based on Investigator judgment:

- Increase in ALT level ≥3 x ULN to ≤5 x ULN and bilirubin ≤2 x ULN (unless the patient has documented Gilbert's disease). The IMP can be resumed at the dose of 150 mg q2w only after the ALT has returned to a value <3 ULN and all requirements for resumption of study drug administration are met (see Section 10.2.4 and Appendix L).
- Decrease in neutrophil count to a level between 500/mm3 to <1000/mm3 without signs and symptoms of a potential infection. The IMP can be resumed at the dose of 150 mg q2w only after the neutrophils have returned to a value ≥1000/ mm^3 and all requirements for resumption of study drug administration are met (see Section 10.2.5 and Appendix L).
- Decrease in platelet count to between 50 000 cells/mm3 to < 100 000 cells/mm3 without spontaneous bleeding. The IMP can be resumed at the dose of 150 mg q2w only after the platelet count is ≥100 000/mm^3 and all requirements for resumption of study drug administration are met (See Section 10.2.6 and Appendix L).
- Infections requiring oral or parenteral treatment with antibacterial, antiviral and/or antifungal agents (See Section 10.2.1 for additional guidance)
- Surgery requiring temporary treatment discontinuation of biologic DMARD as per applicable guidelines

If the dose is reduced to 150 mg q2w the reduced dose will be maintained for the whole duration of the treatment period.

The IMP can be temporarily discontinued for ≤59 days (3 IMP doses can be missed).

Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring.

If the restart of the IMP occurs later than 38 days since the last IMP dose (2 IMP doses were already missed), the IMP has to be administered at the study site and the patient to be observed for 30 minutes for any medical events.

NOTE: in case of prolonged decreased neutrophil count to a level between 500/mm3 to <1000/mm3 without signs and symptoms of a potential infection and/or prolonged increased ALT level ≥3 x ULN to ≤5 x ULN detailed work-up should be performed before sarilumab is reinitiated to rule out other potential causes of neutropenia or ALT elevation.

11.2 PERMANENT TREATMENT DISCONTINUATION WITH INVESTIGATIONAL PRODUCT(S)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

11.2.1 List of criteria for definitive treatment discontinuation

The patients may withdraw from treatment with 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 reasons for treatment discontinuation and this should be documented in the e-CRF.

Study drug will be permanently discontinued in case of the following events:

- Confirmed diagnosis of opportunistic infection based on the investigator's assessment following diagnostic workups and expert consultations
- Active tuberculosis:
  - the diagnosis can be made either on symptoms or on a chest radiograph suggestive of active TB. Patients should be referred to appropriate medical specialists and whenever possible, culture confirmation of disease should be obtained and recorded in the e-CRF.
- The patient is at risk through close contact with a person with active TB and the patient refuses to undergo TB evaluation.
- Culture positive for non-tuberculosis mycobacteria
- Symptoms of systemic hypersensitivity or anaphylactic reactions.
- Severe neurologic disease such as demyelinating disease or PML.
- Significant laboratory abnormalities:
  - ALT> 5xULN or ALT>3xULN with concomitant total bilirubin >2xULN (unless patient with documented Gilbert´s syndrome)
  - neutrophil count <500/mm^3, or neutrophil count <1000/mm^3 with evidence of infection

- platelet count <50 000/mm^3, or platelet count <100 000/mm^3 with evidence of bleeding (see Section 10.2).

- Conversion to HIV positive status
- Acute renal failure
- Pregnancy in female participant.
- Use of any biologic DMARDs other than IMP, or use of any JAK inhibitor
- For EFC13752 patients: use of any non-biologic DMARDs
- Any adverse events, per investigator judgment, that may jeopardize the patient safety.

11.2.2 Handling of patients after permanent treatment discontinuation

Patients will be followed up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last:

- If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedures normally planned for the end of treatment visit and the follow up visit 6 weeks later.

All permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages when considered as confirmed.

11.3 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:

- If possible, the patients are assessed using the procedure normally planned for the end-of treatment visit and post treatment safety follow-up visit.

For patients who fail to return to the site, the Investigator should make the best effort to re-contact the patient (eg, contacting patient's family or private physician, review available registries or health care database), 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 enrolled again (treated) in the study. Their inclusion and treatment number must not be re-used.

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

It is preferred that all study visits take place in the morning. Some visits that include only scheduled blood sampling (V3, V5, V6.1) (Week 2, Week 6, and Week 10) can be scheduled as Home Visits or clinic visits.

Patients will be considered as having completed their treatment per protocol and should complete the end of treatment visit (EOT):

- At Week 264, if sarilumab has been commercialized in their country at that time. EOT visit should be performed instead of Week 264 visit and the assessments defined in the flowchart (Section 1.2.1, Section 1.2.2) should be completed.
- At any visit after Week 264 once sarilumab is commercialized in their country (applicable for patients in the countries where commercial sarilumab is not available at the time the patients completed their Week 264). Some of the assessments are NOT required at EOT for these patients; please refer to the flowchart (Section 1.2.1, Section 1.2.2) for details.
  - When commercialization occurs in a given country, investigators in that country will be alerted by the Sponsor and they will inform their patients during the next scheduled study visit that their subsequent visit 12 weeks later will be the EOT visit.
- At any visit after Week 264 at the time the study is closed in 2020 in countries where commercialization has still not occurred. Some of the assessments are NOT required at EOT for these patients; please refer to the flowchart (Section 1.2.1, Section 1.2.2) for details.
  - EOT visits for all patients remaining in the study at that time will occur at scheduled clinic visits over a 3-month period in order to stagger the completion of EOT visits across the study, and allow the completion of the 6-week follow up period for all patients prior to study closure. Investigators will be alerted by the Sponsor that the study closure is approaching and they will inform their patients during the next scheduled study visit that their subsequent visit 12 weeks later will be the EOT visit.
- At Week 264, for patients in the UK no matter when the sarilumab is commercially available in the country. EOT visit should be performed instead of Week 264 visit and assessments defined in the flowchart (Section 1.2.1, Section 1.2.2) should be completed.

If a patient is permanently and prematurely discontinued from treatment, all assessments planned at the end of treatment visit (EOT) should be performed. Some assessments at EOT are not required if the EOT visit occurs after Week 264, as indicated in the flowchart.

The safety follow-up visit should be performed six weeks from the end of treatment for all patients including those who discontinued before the planned end of treatment with the following exception:

- In patients who complete sarilumab treatment per protocol in countries where sarilumab is commercially available the post treatment follow-up visit may be cancelled if the patient initiates treatment with commercial sarilumab during the post treatment follow-up period. However, in this case, a telephone contact must be established with the patient to capture all AEs occurring up to the 1st administration of commercial sarilumab.

From Week 24 (Visit 8) onwards, some patients may participate in the PFS-S sub-study. No details of the sub-study assessments are described in this section. Please refer to the Appendix R for all information related to the sub-study assessments for these patients.

12.1.1 Visit 1: Screening Visit (D-7 to D-1)

A Screening Visit will only be completed by patients enrolling in the LTS11210 study from ACT11575 or EFC11072 Part A and Part B Cohort 1.

A specific written informed consent form (WICF) should be signed and dated to enter the LTS11210 prior to any screening assessment.

The majority of the screening assessments and labs procedures for this study correspond to the last treatment visit in the study EFC11072 or ACT11575.

The patient will be proposed to enter this study if eligible. If not eligible or unwilling to enter this long term study then he or she will have a follow-up visit 6 weeks after the completion of the study EFC11072 or ACT11575.

The following items will then be checked and recorded:

Assess eligibility by review of inclusion/exclusion criteria.

- Prior and current medication dosage to confirm inclusion and exclusion criteria.
- Previous medical and surgical history: record only new medical and surgical history that has occurred since the randomization visit in study EFC11072, or ACT11575
- Record demographic information.
- History of alcohol and illicit drug use and smoking history.
- For patients entering LTS11210 from Part A of EFC11072 or ACT11575, complete SF-36 questionnaire.

The following will be obtained from the End of Treatment visit in the study EFC11072 or ACT11575:

- Perform a physical examination.
- Record vital signs including body temperature, blood pressure and Heart Rate.
- Record body weight (kg).
- (Fasting) blood for clinical laboratory determinations including hematology, clinical chemistry profile, LFTs and lipids.

- Obtain urine for urinalysis (dipstick) for: specific gravity, pH, glucose, blood, ketones, proteins, bilirubin, urobilinogen, nitrate, leukocytes. If positive for proteins, microscopic analysis will be performed by central laboratory.
- Obtain urine for pregnancy test if female of child bearing potential.
- Obtain 12 – lead ECG
- Perform tuberculosis assessments
- Perform a complete joint examination to assess tender and swollen joints
- Ask the patient to complete relevant questionnaires: HAQ, patient's global assessment, patient's pain questionnaire.
- Ask the patient to complete a sleep questionnaire, the FACIT-Fatigue, WPAI, and for EFC11072 Part B patients, the SF-36.
- Complete the physician global assessment.
- Obtain blood sample for acute phase reactants: hs-CRP. The investigator, patient and sponsor will be blind to the results of the hs-CRP at screening and at baseline. The investigator is advised not to do a local CRP testing unless needed for safety reasons.
- Obtain blood sample for PK (sarilumab), Serum IL-6, and anti-sarilumab antibody.
- Obtain serum sample for future biomarker tests
- ANA (if ANA titer is >1:160 obtain Anti-ds DNA).
- X-rays of hand and feet (applicable to patients who completed EFC11072 Part B

In addition:

- Schedule an appointment for Visit 2 (D1) Week 0.

12.1.2 Baseline (D1) (WK0)

12.1.2.1 Visit 2: Patients enrolling from ACT11575 or EFC11072 Part A or Part B Cohort 1

The following assessments will be completed at Visit 2 by patients enrolling in the LTS11210 study from ACT11575 or EFC11072 Part A and Part B Cohort 1 only.

The Investigator will check the inclusion criteria. For those patients who are eligible the Investigator or designee will:

- Enquire regarding AE/SAEs.
- Complete assessment for TB: sign and symptom of TB or contact with any person with TB.
- Record vital sign including body temperature, blood pressure, and HR.
- Record body weight in Kg.
- Reconfirm eligibility by review of Inclusion/Exclusion criteria with particular attention to:

- Exclusion criteria (see Section 7.3) and co-medication use.
- Record all medication use with start date and dose in the patient's CRF.
- Perform a complete joint examination to assess tender and swollen joints.
- Ask the patient to complete relevant questionnaires: HAQ, patient's global assessment, patient's pain questionnaire.
- Complete the physician global assessment.
- Obtain blood sample for acute phase reactant: hs-CRP. The investigator, patient and sponsor will be blind to the results of the hs-CRP at screening and at baseline. The Investigator is advised not to do a local CRP testing unless needed for safety reasons.
- Obtain blood sample for rheumatoid factor (RF).
- Obtain blood sample for haematology and LFTs.
- Obtain whole blood sample for RNA.
- Call IVRS and receive Medication Pack number assignment from IVRS.
- Dispense the Investigational Product (4 weeks supply) to the patient and provide instructions on preparation and self-injection and dosing. This training must be documented in the patients study file. If the patient is unable or unwilling to administer study drug, arrangements must be made for qualified site personnel and/or caregiver to administer study drug at weekly intervals or specified dose interval by the doctor, including the doses that are not scheduled to be given at the study site.
- The investigator should check the results of the LFTs and neutrophil count after every laboratory visit and take any necessary action to ensure patient safety, including, per protocol-specified rules for dose reduction, and permanent treatment discontinuation.
- The study coordinator or designee will administer the subcutaneous injection of sarilumab comprising of the initial dose at the study office and will observe the patient for 30 minutes for any medical events.
- Patients will be provided with diaries to record medical events pertaining to injections performed at home (date, time, injection location; and local reaction if any).
- Schedule an appointment for Visit 3 (D15±3D) Week 2. This visit can be done as Home Visit at the patient request; and scheduled an appointment for Visit 4 as well if Visit 3 is planned as a Home Visit.

12.1.2.2 Visit 1/Visit 2: Patients enrolling From EFC10832, SFY13370, EFC13752 and EFC11072 Part B Cohort 2

The following assessments will be completed at Visit1/Visit 2 by patients enrolling in the LTS11210 study from EFC10832, SFY13370, EFC13752 or EFC11072 Part B Cohort 2.

A specific written informed consent form (WICF) should be signed and dated to enter the LTS11210 prior to any assessment.

The patient will be proposed to enter this study if eligible. If not eligible or unwilling to enter this long term study then he or she will have a follow-up visit 6 weeks after the completion of the study EFC11072, SFY13370, EFC10832, or EFC13752.

The following V1/V2 assessments and lab procedures for this study will be obtained from the End of Treatment visit in the study EFC11072, SFY13370, EFC10832, or EFC13752. Results of these assessments (if available) should be reviewed prior to patient´s inclusion in the study as a part of eligibility assessment:

- The Investigator or designee will enquire regarding AE/SAEs
- Physical examination
- Vital signs including body temperature, blood pressure and heart rate
- Body weight (kg).
- Clinical laboratory determinations including hematology, clinical chemistry profile, LFTs and lipids.
- Results of urinalysis (dipstick) for: specific gravity, pH, glucose, blood, ketones, proteins, bilirubin, urobilinogen, nitrate, leukocytes (to be included in eligibility assessment). If positive for proteins, results of microscopic analysis performed by central laboratory.
- Results of pregnancy test if female of child bearing potential
- 12 – lead ECG
- Tuberculosis assessments
- Completed joint examination assessing tender and swollen joints
- Completed relevant questionnaires: HAQ, patient's global assessment, patient's pain questionnaire, physician global assessment.
- Completed health economic assessment questionnaires.
- Laboratory results for acute phase reactants: hs-CRP. The investigator, patient and sponsor will be blind to the results of the hs-CRP at Visit V1/V2. The investigator is advised not to do a local CRP testing unless needed for safety reasons.
- Blood sample for PK (sarilumab), Serum IL-6 (for EFC11072 patients), and anti-sarilumab antibody.
- Serum sample for future biomarker tests (except EFC13752 patients)

- Laboratory results for rheumatoid factor (RF).
- Laboratory results for ANA (if ANA titer is >1:160 obtain Anti-ds DNA).
- X-rays of hand and feet (applicable to patients who completed EFC11072 Part B (Cohort 2 and Cohort 1 selected dose arms).

The following items will then be checked to assess eligibility and will be recorded in eCRF:

- Prior and current medication dosage to confirm inclusion and exclusion criteria.
- Previous medical and surgical history (NOTE: no record is needed in eCRF): record only new medical and surgical history that has occurred since the randomization visit in study EFC11072, SFY13370, EFC10832, or EFC13752.
- Demographic information.
- History of alcohol and illicit drug use and smoking history.

If eligibility confirmed:

- The Investigator or designee will call IVRS and receive Medication Pack number assignment from IVRS.
- The Investigational Product (4 weeks supply) will be dispensed to the patient and instructions provided on preparation and self-injection and dosing. This training must be documented in the patients study file. If the patient is unable or unwilling to administer study drug, arrangements must be made for qualified site personnel and/or caregiver to administer study drug at weekly intervals or specified dose interval by the doctor, including the doses that are not scheduled to be given at the study site.
- The study coordinator or designee will administer the subcutaneous injection of sarilumab comprising of the initial dose at the study office and will observe the patient for 30 minutes for any medical events.
- Whole blood sample for RNA expression (for EFC10832 and EFC11072 patients only)
- Patients will be provided with diaries to record medical events pertaining to injections performed at home (date, time, injection location; and local reaction if any).
- An appointment for Visit 3 (D15±3D) Week 2 will be scheduled. This visit can be done as Home Visit at the patient request; and schedule an appointment for Visit 4 as well if Visit 3 is planned as a Home Visit.
- The Investigator should check the results of the LFTs, neutrophil and platelet counts as soon as received and take any necessary action to ensure patient safety, including per protocol-specified rules for dose reduction, and permanent treatment discontinuation.

12.1.3 Visit 3: Home visit On-treatment/Week 2 (D15 ±3D)

This visit can be performed at home.

This visit will include:

- Blood collection for laboratory determinations using the designated central laboratory: hematology and LFTs
- NOTE: For all patients, a CBC test must be performed before or at Visit 3, but not earlier than the 12th day after the first dose of IMP administration (using either designated central laboratory or local laboratory facility) in order to confirm that the neutrophil and/or platelet count(s) are not within the protocol-defined limits for temporary, or permanent discontinuation of study drug.
- For ACT11575, EFC10832 and EFC11072 patients: Collection of whole blood for RNA expression at site visit only; cancel RNA collection if home visit.
- Collection of serum for future biomarker tests (except EFC13752 patients).
- Inquiry regarding AE/SAEs
- The Investigator should check the results of the LFTs, neutrophil and platelet counts as soon as received and take any necessary action to ensure patient safety, including per protocol-specified rules for dose reduction, and permanent treatment discontinuation.

12.1.4 Visit 4: On-treatment/Week 4 (D29, ±3D)

The Investigator or designee will:

- Inquire regarding AE/SAEs.
- Check compliance to the study drug and concomitant medication and record any changes in the patient's CRF.
- Record vital signs including body temperature, blood pressure and HR and weight.
- Perform tuberculosis assessment. In case of suspicion of tuberculosis, refer the patient to a TB specialist for complete examination and additional work-up (see specific instructions in Section 10.2.1).
- Obtain (fasting) blood for complete clinical laboratory determinations including: hematology, and LFTs and lipids.
- Before dosing obtain blood sample for PK (sarilumab), serum IL-6.
- Obtain blood sample for acute phase reactant: hs-CRP.
- Obtain urine for pregnancy test for female of childbearing potential.
- Perform a complete joint examination to assess tender and swollen joints.
- Ask the patient to complete relevant questionnaires: HAQ, patient's global assessment, patient's pain questionnaire.

- Complete the physician global assessment.
- Dispense Investigational Product (4-week supply) and remind instructions on self-injection and dosing.
- The study coordinator or designee will administer the subcutaneous injection (if 14 ± 3 days from the last administration), will observe the patient for 30 minutes.
- Schedule appointment for Visit 5 (D43 ± 3D) either on site or as Home Visit and schedule an appointment for Visit 6 as well if Visit 5 is planned as a Home Visit.
- Provide self-injection diary
- The Investigator should check the results of the LFTs, neutrophil and platelet counts as soon as received and take any necessary action to ensure patient safety, including per protocol-specified rules for dose reduction, and permanent treatment discontinuation.

12.1.5 Visit 5, Home Visit: On-treatment/Week 6 (D43 ±3D)

This visit can be performed at home.

This visit will include:

- Blood collection for laboratory determinations using the designated central laboratory: hematology and LFTs
- Inquiry regarding AE/SAEs.

The Investigator should check the results of the LFTs, neutrophil and platelet counts as soon as received and take any necessary action to ensure patient safety, including per protocol-specified rules for dose reduction, and permanent treatment discontinuation.

12.1.6 Visit 6, on-treatment/Week 8 (D57±3D)

The Investigator will:

- Check compliance to the study drug and concomitant medication and record any changes in the patient's CRF.
- Record vital signs including body temperature, blood pressure and HR and weight.
- Tuberculosis assessment. In case of suspicion of tuberculosis, refer the patient to a TB specialist for complete examination and additional work-up (see specific instructions in Section 10.2.1).
- Inquire regarding AE/SAEs.
- Obtain (fasting) blood for complete clinical laboratory determinations including: hematology, clinical chemistry profile, LFTs and lipids.
- Obtain blood sample for acute phase reactant: hs-CRP.
- Obtain urine for urinalysis (dipstick).
- Obtain urine for pregnancy test for female of child bearing potential.

- Perform a complete joint examination to assess tender and swollen joints.
- Ask the patient to complete relevant questionnaires: HAQ, patient's global assessment, patient's pain questionnaire.
- Complete the physician global assessment.
- Dispense Investigational Product (4-week supply) and remind instructions on self-injection and dosing; and provide self-injection diary.
- The study coordinator or designee will administer the subcutaneous injection (if 14±3 days from the last administration), and will observe the patient for 30 minutes.
- Schedule appointment for Visit 6.1 (D71 ± 3D) either on site or as Home visit and schedule Visit 7 (D85 ±3D).
- The Investigator should check the results of the LFTs, neutrophil and platelet counts as soon as received and take any necessary action to ensure patient safety, including per protocol-specified rules for dose reduction, and permanent treatment discontinuation.

12.1.7 Visit 6.1, Home Visit: On-treatment/Week 10 (D71 ±3D)

This visit can be performed at home.

This visit will include:

- Blood collection for laboratory determinations using the designated central laboratory: hematology and LFTs
- Inquire regarding AE/SAEs

The Investigator should check the results of the LFTs, neutrophil and platelet counts as soon as received and take any necessary action to ensure patient safety, including per protocol-specified rules for dose reduction, and permanent treatment discontinuation.

12.1.8 Visit 7: On-treatment/ Week 12 (D85±3D)

The Investigator will:

- Check compliance to the study drug and concomitant medication and record any changes in the patient's CRF.
- Record vital signs including body temperature, blood pressure and HR and body weight.
- Tuberculosis assessment. In case of suspicion of tuberculosis, refer the patient to a TB specialist for complete examination and additional work-up (see specific instructions in Section 10.2.1).
- Inquire regarding AE/SAEs.
- Obtain (fasting) blood for complete clinical laboratory determinations including: hematology, clinical chemistry profile, LFTs, lipids profile.

- Save an aliquot of serum (5 mL) for storage for future biomarkers (except for EFC13752 patients).
- Obtain blood sample for acute phase reactant: hs-CRP.
- Before dosing obtain blood sample for PK (sarilumab), serum IL-6, and anti-sarilumab antibody.
- Obtain urine for urinalysis (dipstick).
- Obtain urine sample for urine pregnancy test for female of child bearing potential. The patients should be instructed to do the urine pregnancy test at home on a monthly basis during the intervals in between on-treatment clinic visits for the duration of the treatment period. In case of a positive pregnancy test, the patient should be advised to stop the IMP and to contact immediately her study doctor.
- Perform a complete joint examination to assess tender and swollen joints.
- Ask the patient to complete relevant questionnaires: HAQ, patient's global assessment, patient's pain questionnaire.
- Ask the patient (except for SFY13370 and EFC13752 patients) to complete health economic assessments as per initial study (See Section 1.2).
- Complete the physician global assessment.
- Dispense Investigational Product (12-week supply) and remind instructions on self-injection and dosing; and provide self-injection diary.
- The study coordinator or designee will administer the subcutaneous injection (if 14±3 days from last administration) and will observe the patient for 30 minutes.
- Dispense urine pregnancy test kit for monthly urine pregnancy test (3 month supply).
- Schedule appointment for Visit 8 (D169 ±3D).
- The Investigator should check the results of the LFTs, neutrophil and platelet counts as soon as received and take any necessary action to ensure patient safety, including per protocol-specified rules for dose reduction, and permanent treatment discontinuation.

Patients will have on treatment visit every 12 weeks starting from Week 24 to Week 96 and then every 24 weeks until EOT. Each visit can be done within ± 3days.

12.1.9 Visit 8 (Week 24) to Visit 14 (Week 96) and Visit 16 (Week 120), Visit 18 (Week 144), Visit 20 (Week 168), Visit 22 (Week 192), Visit 24 (Week 216), Visit 26 (Week 240), Visit 28 (Week 264): On treatment visits from Week 24 to Week 264

This section refers to on-treatment visits with clinical assessments from week 24 up to the end of the initial 264-week period of the study (excluding the IMP dispensing visits).

The Investigator will:

- Check compliance to the study drug and concomitant medication and record any changes in the patient's CRF.

- Record vital signs including body temperature, blood pressure, HR and body weight.
- Physical examination will be done only at weeks: 48, 96, 144, 192, 240 and 264.
- Tuberculosis assessment. In case of suspicion of tuberculosis, refer the patient to a TB specialist for complete examination and additional work-up (see specific instructions in Section 10.2.1).
- Inquire regarding AE/SAEs.
- Obtain (fasting) blood for complete clinical laboratory determinations including: hematology, clinical chemistry profile, LFTs, lipids profile.
- Save an aliquot of serum (5mL) for storage for future biomarkers at Week 48 (except EFC13752 patients).
- Obtain blood sample for acute phase reactant: hs-CRP.
- Obtain blood sample for rheumatoid factor at week 48, 96, 144, 192, 240 and 264.
- Before dosing obtain sample for serum IL-6 only at week 24, 36 and 48.
- Before dosing, obtain serum sample for PK (sarilumab) and for anti-sarilumab antibody.
- Obtain blood sample for ANA at Week 48, 96, 144, 192, 240 and 264 or sooner if clinically indicated.
- Obtain urine for dipstick urinalysis.
- Obtain urine sample for urine pregnancy test for female of child bearing potential. The patients should be instructed to do the urine pregnancy test at home on a monthly basis during the intervals in between on-treatment clinic visits for the duration of the treatment period. In case of a positive pregnancy test, the patient should be advised to stop the IMP and to contact immediately her study doctor.
- X-Ray of the hands and feet (only for patients who completed EFC11072 Part B (Cohort 2 and Cohort 1 selected dose arms)) at week 48, 96, 144, 192 (±14 days for each evaluation), and transfer images to the central readers.
- ECG at week 48, 96, 144, 192, 240 and 264.
- Perform a complete joint examination to assess tender and swollen joints.
- Ask the patient to complete relevant questionnaires: HAQ, patient's global assessment, patient's pain questionnaire.
- Ask the patient (except for SFY13370 and EFC13752 patients) to complete health economic assessments as per initial study (See Section 1.2).
- Complete the physician global assessment.
- Dispense Investigational Product (12-week supply) and remind instructions on self-injection and dosing; and provide self-injection diary.
- The study coordinator or designee will administer the subcutaneous injection (if 14±3 days from last administration) and will observe the patient for 30 minutes.
- Dispense urine pregnancy test kits for monthly urine pregnancy test.

- Schedule appointment for next visit.
- The Investigator should check the results of the LFTs, neutrophil and platelet counts as soon as received and take any necessary action to ensure patient safety, including per protocol-specified rules for dose reduction, and permanent treatment discontinuation.

12.1.10 Visit 15 (Week 108), Visit 17 (Week 132), Visit 19 (Week 156), Visit 21 (Week 180), Visit 23 (Week 204), Visit 25 (Week 228), Visit 27 (Week 252), Visit 29 (Week 276), Visit 31 (Week 300), Visit 33 (Week 324), Visit 35 (Week 348), Visit 37 (Week 372), Visit 39 (Week 396), Visit 41 (Week 420), Visit 43 (Week 444), Visit 45 (Week 468), Visit 47 (Week 492): IMP dispensing visits in between 24-week on-treatment visits (after Week 96)

This section refers to the IMP dispensing visits that will occur every 24 weeks from week 108 to week 492, alternating with the visits at which clinical assessments are performed.

After Week 96, at 12-week intervals in between the q 24-week on-treatment visits the Investigator will:

- Check compliance to the study drug and concomitant medication and record any changes in the patient's CRF.
- Obtain blood sample for hematology and LFTs (applicable for Portugal and Sweden only; no PT required after Week 264).
- Inquire regarding AE/SAEs.
- Dispense Investigational Product (12-week supply) and remind instructions on self-injection and dosing; and provide self-injection diary.
- Schedule appointment for next visit.

12.1.11 Visit 30 (Week 288), Visit 32 (Week 312), Visit 34 (Week 336), Visit 36 (Week 360), Visit 38 (Week 384), Visit 40 (Week 408), Visit 42 (Week 432), Visit 44 (Week 456), Visit 46 (Week 480), Visit 48 (Week 504): On treatment visits from Week 288 to week 504

This section refers to on-treatment visits with less complex clinical assessments, for patients who are continuing in the study after week 264 because sarilumab is not yet commercialized in their country.

The Investigator will:

- Check compliance to the study drug and concomitant medication and record any changes in the patient's CRF.
- Record vital signs including body temperature, blood pressure, HR and body weight.
- Physical examination will be done only at weeks: 288, 336, 384, 432 and 480.
- Tuberculosis assessment. In case of suspicion of tuberculosis, refer the patient to a TB specialist for complete examination and additional work-up (see specific instructions in Section 10.2.1).

- Inquire regarding AE/SAEs.
- Obtain (fasting) blood for complete clinical laboratory determinations including:
  - hematology
  - clinical chemistry profile
  - LFTs (no PT required)
  - lipids (only TC, HDL cholesterol, LDL cholesterol, triglycerides) will only be done at weeks: 288, 336, 384, 432 and 480.
- Obtain blood sample for acute phase reactant: hs-CRP.
- Before dosing, obtain serum sample for PK (sarilumab) and for anti-sarilumab antibody.
- Obtain blood sample for ANA at week 288, 336, 384, 432 and 480, or sooner if clinically indicated.
- Obtain urine sample for urine pregnancy test for female of child bearing potential. The patients should be instructed to do the urine pregnancy test at home on a monthly basis during the intervals in between on-treatment clinic visits for the duration of the treatment period. In case of a positive pregnancy test, the patient should be advised to stop the IMP and to contact immediately her study doctor.
- Perform a complete joint examination to assess tender and swollen joints. Only the 28 joints required for DAS28 calculation need to be evaluated (see Appendix B).
- Ask the patient to complete patient's global assessment.
- Dispense Investigational Product (12-week supply) and remind instructions on self-injection and dosing; and provide self-injection diary.
- The study coordinator or designee will administer the subcutaneous injection (if 14±3 days from last administration) and will observe the patient for 30 minutes.
- Dispense urine pregnancy test kits for monthly urine pregnancy test.
- Schedule appointment for next visit.
- The Investigator should check the results of the LFTs, neutrophil and platelet counts as soon as received and take any necessary action to ensure patient safety, including per protocol-specified rules for dose reduction, and permanent treatment discontinuation.

12.1.12 Visit 49: End of treatment (EOT)

The investigator will:

- Check compliance to the study drug and concomitant medication and record any changes in the patient's CRF.
- Record vital signs including body temperature, blood pressure, HR and body weight.
- Perform physical examination

- Perform tuberculosis assessment. In case of suspicion of tuberculosis, refer the patient to a TB specialist for complete examination and additional work-up (see specific instructions in Section 10.2.1).
- Inquire regarding AE/SAEs.
- Obtain blood sample for acute phase reactant: hs-CRP.
- Obtain serum sample for PK (sarilumab) and for anti-sarilumab antibody.
- Obtain blood sample for ANA
- Obtain urine sample for urine pregnancy test for female of child bearing potential.

In addition:

– If the **EOT is prior to or including Week 264**, the investigator will also:
  - Obtain (fasting) blood for complete clinical laboratory determinations including:
    - hematology
    - clinical chemistry profile
    - LFTs
    - lipids profile.
  - Obtain blood sample for rheumatoid factor.
  - Obtain urine for dipstick urinalysis.
  - Perform ECG.
  - Perform a complete joint examination to assess tender and swollen joints.
  - Ask the patient to complete relevant scales and questionnaires: patient's global assessment, HAQ, patient's pain questionnaire.
  - Complete the physician global assessment
  - Ask the patient (except for SFY13370 and EFC13752 patients) to complete health economic assessments as per initial study (See Section 1.2).
  - Arrange X-Ray of the hands and feet (only for patients who completed EFC11072 Part B (Cohort 2 and Cohort 1 selected dose arms)) when EOT is no later than the Week 192 visit.

– If the **EOT is after Week 264**, the investigator will also:
  - Obtain (fasting) blood for complete clinical laboratory determinations including:
    - hematology
    - clinical chemistry profile
    - LFTs (PT is not required)
    - lipids profile (only TC, HDL cholesterol, LDL cholesterol, triglycerides).

- Perform a complete joint examination to assess tender and swollen joints. Only the 28 joints required for DAS28 calculation need to be evaluated (see Appendix B).
- Ask the patient to complete patient's global assessment.

The investigator should schedule appointment for follow-up visit.

The Investigator should check the results of the LFTs, neutrophil and platelet count as soon as received and take any necessary action to ensure patient safety.

12.1.13 Visit 50: Post Treatment safety follow-up visit

Patients that discontinued prematurely before the planned end of treatment, or who completed their treatment per protocol should have this visit performed 6 weeks from end of treatment visit with the following exception:

– In patients who complete sarilumab treatment per protocol in countries where sarilumab is commercially available the post treatment follow-up visit may be cancelled if the patient initiates treatment with commercial sarilumab during the post treatment follow-up period. However, in this case, a telephone contact must be established with the patient to capture all AEs occurring up to the 1st administration of commercial sarilumab.

The Investigator will:

- Record vital signs including body temperature, blood pressure and HR and weight.
- Perform tuberculosis assessment. In case of suspicion of tuberculosis, refer the patient to a TB specialist for complete examination and additional work-up (see specific instructions in Section 10.2.1).
- Inquire regarding AE/SAEs and concomitant medications.
- Obtain urine for pregnancy test for female of child bearing potential.
- Obtain serum sample for PK (sarilumab) and for anti-sarilumab antibody.

12.2 DEFINITION OF SOURCE DATA

The source data will be the following:

- Chest X-ray or signed documented X-ray and reports
- Joints X-rays
- HAQ-DI questionnaires
- Patients assessments of pain
- Patient's global assessment of disease activity
- Physician's global assessment of disease activity
- Tender/painful and swollen joint counts

- Patient diaries
- Central and local lab reports
- Completed FACIT-Fatigue
- Health economics assessments and PROs
- ECG tracings and reports

13 STATISTICAL CONSIDERATIONS

13.1 DETERMINATION OF SAMPLE SIZE

The number of patients to participate in this extension study will be approximately 2000.

13.2 ANALYSIS ENDPOINTS

13.2.1 Demographic and baseline characteristics

Baseline for this study is defined to be the baseline measurement from the previous (initial) study.

13.2.1.1 Demographic and baseline characteristics

Demographic characteristics

The following demographic characteristics will be summarized:

- Gender (male, female)
- Race (Caucasian/White, Black, Asian/Oriental, other)
- Ethnicity (Hispanic, Not Hispanic)
- Region (Western countries, South America, Rest of the World)
- Age (years)
- Age group (<65, ≥65 to ≤75, ≥75 years)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI group (<25, ≥25 and <30, ≥30 kg/m^2).

Disease characteristics at baseline

The following baseline disease characteristics will be summarized:

- Time since diagnosis of RA (Years)
- Rheumatoid factor (Positive: ≥1 IU/mL, negative: <1 IU/mL)
- Anti CCP (positive, negative)
- Prior biologic DMARD use for RA
- Smoking history
- Alcohol use

In addition, the summary of baseline values for clinical signs and symptoms and quality of life assessments will be presented in the summary tables for these data.

13.2.1.2 Concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD). Concomitant medications are those patients used at any time during the study treatment period, from the first investigational product intake to the end of the follow-up period.

13.2.2 Safety endpoints

The safety variables include adverse events, clinical laboratory parameters, vital signs, and ECG. The primary safety analysis variables are adverse events.

The same observation period (defined below) will be used for all safety observations.

Observation period

The observation of safety data will be as follows:

- The treatment-emergent observation period is defined as the time from the first dose of sarilumab in this study LTS11210 up to last dose of sarilumab + 60 days.
- The post-study period is defined as the time after the last dose of sarilumab + 60 days.

13.2.2.1 Adverse events

Adverse event observation period

The adverse event observations are per the observation period defined above.

13.2.2.2 Laboratory safety variables

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

13.2.2.3 Vital signs

Vital signs variables include: weight, systolic blood pressure, diastolic blood pressure, temperature, and heart rate.

13.2.2.4 Electrocardiogram variables

A standard 12-lead ECG will be performed and will be determined using centralized automatic and manual readings.

ECG parameters include heart rate, PR, QRS, QT as well as QTc (corrected according to Bazett/Fridericia formula).

13.2.3 Efficacy endpoints

The efficacy endpoints as defined in Section 9.1.2 will include:

- ACR20 response over time up to Week 264
- ACR50 and ACR70 response over time up to Week 264
- DAS28 -CRP response over time
- DAS28 remission over time
- EULAR response over time
- Change from baseline in the van der Heijde modified total Sharp score (for patients from Part B of EFC11072 with an end of treatment X-ray evaluation) at weeks 48, 96, 144, 192, or EOT, if EOT is prior to Week 192
- Incidence of radiographic progression of the van der Heijde modified total sharp score at weeks 48, 96, 144, 192, or EOT if EOT is prior to Week 192
- Change from baseline in HAQ-DI over time up to Week 264
- Change from baseline in ACR components up to Week 264. After Week 264, TJC and SJC (both based on 28 joints), patient´s global assessment of disease activity and hs-CRP will still be assessed to calculate DAS28.

13.2.4 Pharmacokinetic and immunogenicity variables

Immunogenicity (anti sarilumab antibody) and pharmacokinetic blood samples (trough concentrations) will be collected according to the study flow chart (Section 1.2). Pharmacokinetic samples will also be collected at or near the onset and completion of the occurrence of a serious adverse event.

13.2.5 Pharmacodynamic/genomics variables

Serum concentrations of IL-6 will be assessed according to the study flow chart (Section 1.2).

13.2.6 Health economic variables

- Change from baseline in SF-36 version 2 scores (2 summary measures: physical component summary score and mental component summary score; 8 domains: physical function, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) over time (for patients from EFC11072, ACT11575 and EFC10832 only)
- Change from baseline in WPAI scores (percent work time missed, percent impairment while working, percent activity impairment, percent overall work impairment) (for patients from EFC11072 and ACT11575 only)

- Change from baseline in the FACIT-Fatigue score over time (for patients from EFC11072, ACT11575 and EFC10832 only)
- Change from baseline in the sleep VAS scale over time (for patients from EFC11072 and ACT11575 only)
- Change from baseline in the WPS-RA scores (3 work productivity related items and 5 home productivity related items over time) (for patients from EFC10832 only)

Health economic variables will be assessed up to Week 264.

13.3 DISPOSITION OF PATIENTS

The total number of patients for each of the following categories will be presented in the clinical study report:

- All screened patients: all patients who have signed the informed consent
- All patients entered in the LTS: all patients who have signed the informed consent and are eligible to enter the study.
- Safety population: defined as all patients entered in the LTS who have received at least 1 dose of the study treatment in the LTS11210,
- Patients who discontinued the treatment and reasons for treatment discontinuation.

The percentage will be calculated using the total number of all patients entered in the LTS as the denominator.

13.4 ANALYSIS POPULATIONS

The primary analysis population is the safety population which is defined as all patients who have received at least 1 dose of the study treatment in the LTS11210.

All safety analyses and efficacy analyses will be performed based on the safety population.

13.5 STATISTICAL METHODS

For patients from EFC11072, ACT11575, EFC10832 and SFY13370 with sarilumab + DMARD therapy in the initial and current studies, all analyses will be performed based on previous treatment prior to enrollment into LTS11210 (placebo, sarilumab 150mg q2w, sarilumab 200mg q2w, other sarilumab (non-selected) doses, and active control treatment) as well as overall in LTS11210, unless otherwise specified. Interim analyses may be performed based on overall sarilumab +DMARD therapy only.

For patients from EFC13752 with sarilumab monotherapy in the initial and current studies, all analyses will be performed based on previous treatment prior to enrollment into LTS11210

(sarilumab 150mg q2w, sarilumab 200mg q2w) as well as overall in LTS11210, unless otherwise specified. Interim analyses may be performed based on overall sarilumab monotheraphy only.

Data analysis results will be presented by sarilumab +DMARD therapy and sarilumab monotherapy in LTS11210 separately. All analyses will be performed in observed cases unless otherwise specified.

13.5.1 Demographic and baseline characteristics

Patient characteristics including demographics, medical history, and subject accountability will be summarized for the safety population. The summaries will consist of descriptive statistics, eg, mean, standard deviation, median, minimum and maximum for quantitative values and counts and percentages for qualitative variables.

13.5.2 Concomitant medications

The concomitant medications will be presented based on the safety population. Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the Anatomic Category (ATC) class (anatomic category) and the first 3 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.

13.5.3 Extent of study treatment exposure and compliance

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

13.5.3.1 Extent of investigational product exposure

Duration of exposure is defined as:

<u>For patients receiving weekly injections at the last injection</u>

[*Date of last injection of the study med*] – [*Date of first injection of the study med*] + 7

<u>For patients receiving biweekly injections at the last injection</u>

[*Date of last injection of the study med*] – [*Date of first injection of the study med*] + 14

Temporary drug discontinuation will be ignored in the above calculation.

Duration of exposure will be summarized by dose and overall using descriptive statistics such as mean, standard deviation, median, minimum and maximum.

The number and percentage of patients exposed of the investigational product will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the statistical analysis plan.

13.5.3.2 Compliance

Treatment compliance is defined as the actual amount of drug taken compared to the scheduled amount of treatment. It is calculated according to the following formula:

100 x *total number of compliant injections administered /* [*nominal number of injections for the duration of exposure*].

A given administration will be considered as noncompliant 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 will be summarized using means, standard deviations, medians, minimums and maximums. In addition, the percentage of patients with <80% treatment compliance will be summarized.

13.5.4 Analyses of safety data

The review of safety and tolerability will be performed based on the safety population, as defined in Section 13.4 . The safety analyses will be presented based on the reported adverse events, clinical laboratory evaluations, vital signs, and 12-lead ECGs.

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

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs and ECG.
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent period, taking into account all evaluations performed during the treatment-emergent period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the treatment-emergent PCSA percentage.

13.5.4.1 Adverse events

Adverse events reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) in effect at sanofi at the time of database lock. Treatment-emergent adverse events (TEAEs) are AEs that developed or worsened or became serious during the TEAE period.

Treatment-emergent adverse events

The TEAE incidence will be presented by System organ class (SOC), High level group term (HLGT), High level term (HLT), and preferred term (PT) sorted in alphabetical order, the number (n) and percentage (%) of patients experiencing a TEAE will be presented. Multiple occurrences of the same event in the same patient will be counted only once in the tables. The denominator is based on the total number of patients in the safety population. In addition, the number of TEAEs (n) will be summarized. Multiple occurrences of the same event in the same patient will all be counted only once in the tables within a treatment group. The TEAE incidence rate adjusted for the total duration of exposure will be provided along with the exposure-adjusted number of TEAEs.

Deaths

The following deaths summary will be generated

- TEAE leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing the number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Serious adverse events

The number and percentage of patients with SAEs will be summarized by primary SOC, HLGT, HLT and PT.

Adverse events leading to treatment discontinuation

The number and percentage of patients with adverse events leading to permanent treatment discontinuation will be summarized by primary SOC, HLGT, HLT, and PT.

Adverse events of special interest (AESI)

AESIs will be flagged using search criteria. If available, a Standard MedDRA Query (SMQ) will be used to search (narrow search). If no SMQ is available, then a Sponsor defined search criteria will be used. The number and percentage of patients with treatment emergent AESIs will be summarized by AESI category and PT.

13.5.4.2 Liver Function Tests

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

A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and Total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

The normalization (to ≤ ULN or return to baseline) of elevated liver function tests will be summarized by categories of elevation (3 x, 5 x, 10 x, 20 x ULN for ALT and AST, 1.5 x ULN for alkaline phosphatase, and 1.5 x and 2 x ULN for total bilirubin), with following categories of normalization: never normalized, normalized after IMP discontinuation. Note that a patient will be counted only under the maximum elevation category.

The incidence of liver related adverse events will be summarized. The selection of PTs will be based on standardized MedDRA query (SMQ) Drug-related hepatic disorder – comprehensive search.

13.5.4.3 Clinical laboratory evaluations

Patients with PCSA for each laboratory test will be identified. The incidence of PCSAs at any time during the TEAE period will be summarized by biological function and treatment received whatever the baseline level and/or according to the following original baseline status categories:

1. normal/missing,
2. abnormal according to PCSA criterion or criteria.

Descriptive statistics will also be used to summarize baseline, raw value, and change from baseline at each visit.

Shift tables showing changes with respect to the normal range between baseline and postbaseline will be provided.

Listings will be provided with flags indicating the out of range values as well as the PCSA values.

13.5.4.4 Vital signs

Vital signs including weight, blood pressure (systolic and diastolic), and heart rate are measured throughout the study. Descriptive statistics will be provided for baseline, raw value, and change from baseline at each visit.

The number and percentage of patients with at least 1 PCSA during the TEAE period will be summarized.

13.5.4.5 Electrocardiogram

12-lead ECG data will be collected throughout the study. Descriptive statistics will be provided for baseline, absolute value, and change from baseline per visit.

The number and percentage of patients with at least 1 PCSA during the TEAE period will be summarized for each ECG parameter.

13.5.5 Analyses of efficacy endpoints

There will be no confirmatory analysis for the efficacy variables. All analysis will be done descriptively on the safety population by visit in observed case, as appropriate.

For categorical variables, for example, percentage of patients who have maintained/reached ACR20 overtime, the number and percentage will be provided from all patients who have data available at that time point, and the 95% confidence intervals will be calculated if appropriate.

For continuous variables, descriptive statistics such as the mean, standard deviation, median, minimum and maximum will be provided. In addition, 95% confidence interval of the mean will be presented. This applies to the original values and change (or percent change) from baseline.

Change from baseline in the van der Heijde modified total Sharp scores (mTSS) will be summarized for patients from EFC11072 Part B only. Descriptive statistics, including the mean, standard deviation, median, minimum and maximum will be provided, along with 95% confidence intervals. The actual values will be similarly summarized.

Radiographic progression of the mTSS is defined as a change from baseline in the mTSS > 0. A change from baseline in the mTSS of less than or equal to zero is considered as no progression. The event of missing a change from baseline in the mTSS will be considered as progression. Summary of incidence of radiographic progression of mTSS will be provided.

Additional sensitivity analyses may be performed if necessary.

13.5.6 Analyses of pharmacokinetic and pharmacodynamic variables

13.5.6.1 Pharmacokinetic descriptive analysis

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

Serum concentrations of bound (serum sarilumab-sIL-6Rα complex) and functional sarilumab were intended to be analyzed in the study. After the completion of EFC11072 Part B study, the Sponsor made the decision to only analyze functional sarilumab concentrations. Serum concentrations of bound sarilumab (serum sarilumab-sIL-6Rα complex) will not be summarized in this study.

13.5.6.2 Immunogenicity variables

Anti-sarilumab antibody (ADA) assay results will be described categorically. The summary will be provided for patients with any positive ADA assay response during the TEAE period. Patients with any positive ADA assay response are defined as:

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

13.5.6.3 Pharmacodynamic descriptive analysis

Serum concentrations of IL-6 will be summarized using arithmetic and geometric means, SD, SEM, CV%, minimum, median, and maximum by dose and visit.

13.5.7 Analyses of quality of life/health economics variables

Change from baseline in the SF36 version 2 scores (2 summary measures and 8 domains) will be summarized using raw value and change from baseline at each visit or study assessment (baseline, endpoint) by dose.

Change from baseline in the 4 WPAI scores will be summarized using raw value and change from baseline at each visit or study assessment (baseline, endpoint) by dose.

Change from baseline in the FACIT-Fatigue score and the sleep VAS will be summarized using raw value and change from baseline at each visit or study assessment (baseline, endpoint) by dose.

Change from baseline in the 8 WPS-RA scores will be summarized using raw value and change from baseline at each visit or study assessment (baseline, endpoint) by dose (for the patients from EFC10832 only).

13.6 DATA HANDLING CONVENTIONS

Missing dates will be handled using conservative approaches, and no imputation will be applied at the data level:

- If the date of the last dose of investigational drug is missing, duration of exposure will be set to missing.
- Handling of PCSAs: If a subject has a missing baseline value, he will be grouped in the category “normal /missing at baseline.” For PCSA with 2 conditions, one based on a change from baseline value or a normal range and the other one on a threshold value, the first condition being missing, the PCSA will be based only on the second condition. For PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold only if the normal range is missing. For example, for eosinophils the PCSA is

>0.5 GIGA/L or > ULN if ULN ≥0.5 GIGA /L. When the ULN is missing, the value 0.5 should be used.

13.7 X-RAY DATA SUMMARY

X-rays are performed in the subset of patients who previously completed EFC11072, Part B. X-ray data will be read in 3 campaigns in order to summarize:

- 2 year data up to Week 48 in LTS11210
- 3 year data up to Week 96 in LTS11210
- 5 year data up to Week 192 in LTS11210

Each campaign will include screening/baseline EFC11072 X-ray data

13.8 INTERIM ANALYSIS

This is an open-label study. Interim reports may be prepared for regulatory submissions or other purposes. However, no alpha adjustment is needed for the final CSR.

14 ETHICAL AND REGULATORY STANDARDS

14.1 ETHICAL PRINCIPLES

This Clinical Trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice (GCP).

14.2 LAWS AND REGULATIONS

This Clinical Trial will be conducted in compliance with all international laws and regulations, and national laws and regulations of the country(ies) in which the Clinical Trial is performed, as well as any applicable guidelines.

14.3 INFORMED CONSENT

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

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

The Informed Consent Form 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.

14.4 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 appropriate Ethics Committee (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 Ethics Committee (IRB/IEC) composition.

The Clinical Trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, Informed Consent Form, Investigator’s Brochure, Investigator’s CV, etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

Investigational Product 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 Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the Clinical Trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC).

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually and a summary of the Clinical Trial's outcome at the end of the Clinical Trial.

15 STUDY MONITORING

15.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

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 Case Report Form [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.

15.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the Case Report Forms. 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, Serious Adverse Event documentation and reporting, AESI documentation and reporting AE documentation, Investigational Product allocation, patient compliance with the Investigational Product regimen, Investigational Product accountability, concomitant therapy use and quality of data.

15.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the Case Report Form entries against the source documents, except for the pre-identified source data directly recorded in the Case Report Form. 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 Case Report Forms (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 rules).

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

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (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.

Should a correction be made, the corrected will be entered in the e-CRF 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 e-CRF.

The computerized handling of the data by the Sponsor after receipt of the CRFs 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 e-CRF.

15.5 USE OF COMPUTERIZED SYSTEMS

Computerized systems used during the different steps of the study are:

- For data management activities: Oracle Clinical (RDC)
- For statistical activities: SAS
- For pharmacovigilance activities: AWARE
- For monitoring activities: IMPACT
- For medical writing activities: Domasys

External data loading is planned for this clinical trial.

16 ADMINISTRATIVE RULES

16.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-Investigator will be provided to the Sponsor prior to the beginning of the Clinical Trial.

16.2 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.

It is recommended that the Investigator retain the study documents at least fifteen (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.

17 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, the CRFs, the Investigator's Brochure and the results obtained during the course of the Clinical Trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Trial.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account.

18 PROPERTY RIGHTS

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

The Investigator shall not 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.

19 DATA PROTECTION

The patient's personal data and Investigator's personal data which may be 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.

20 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 maintaining their own liability insurance policy. An insurance certificate will be provided to the Ethics committees/IRB or Health Authorities in countries requiring this document.

21 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 this 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.

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

22.1 DECIDED BY THE SPONSOR IN THE FOLLOWING CASES:

If the information on the product leads to doubt as to the benefit/risk ratio;

If the Investigator has received from the Sponsor all Investigational Product, means and information necessary to perform the Clinical Trial and has not included any patient after a reasonable period of time mutually agreed upon;

In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the Clinical Trial Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for Good Clinical Practice;

If 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.

22.2 DECIDED BY THE INVESTIGATOR

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed according to applicable regulatory requirements.

23 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a Clinical Study Report and to provide a summary of study results to Investigator;

When the data from all investigational sites have been fully analyzed by the Sponsor, the latter will communicate the results of the Clinical Trial to the Investigator(s).

24 PUBLICATIONS AND COMMUNICATIONS

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

The Study is being conducted at multiple sites; the Sponsor agrees that, consistent with scientific standards, first presentation or publication of the results of the Study shall be made only as part of a publication of the results obtained by all sites performing the Protocol. However, if no multicenter publication has occurred 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, subject to the review procedure set forth herein. The Investigator shall provide the Sponsor with a copy of any such presentation or publication derived from the Study for review and comment at least thirty (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 ninety (90) days, to allow for filing of a patent application or such other 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.

25 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 of the Clinical Trial Protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, 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 Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

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.

26 BIBLIOGRAPHIC REFERENCES

1. Kremer JM, Rationale use of new and existing disease modifying agents in rheumatoid arthritis. Ann Intern Med. 2001;134:695-706

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4. Keystone EC, Kavanaugh AF, Sharp JT, et al: Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: A randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50:1400-11.

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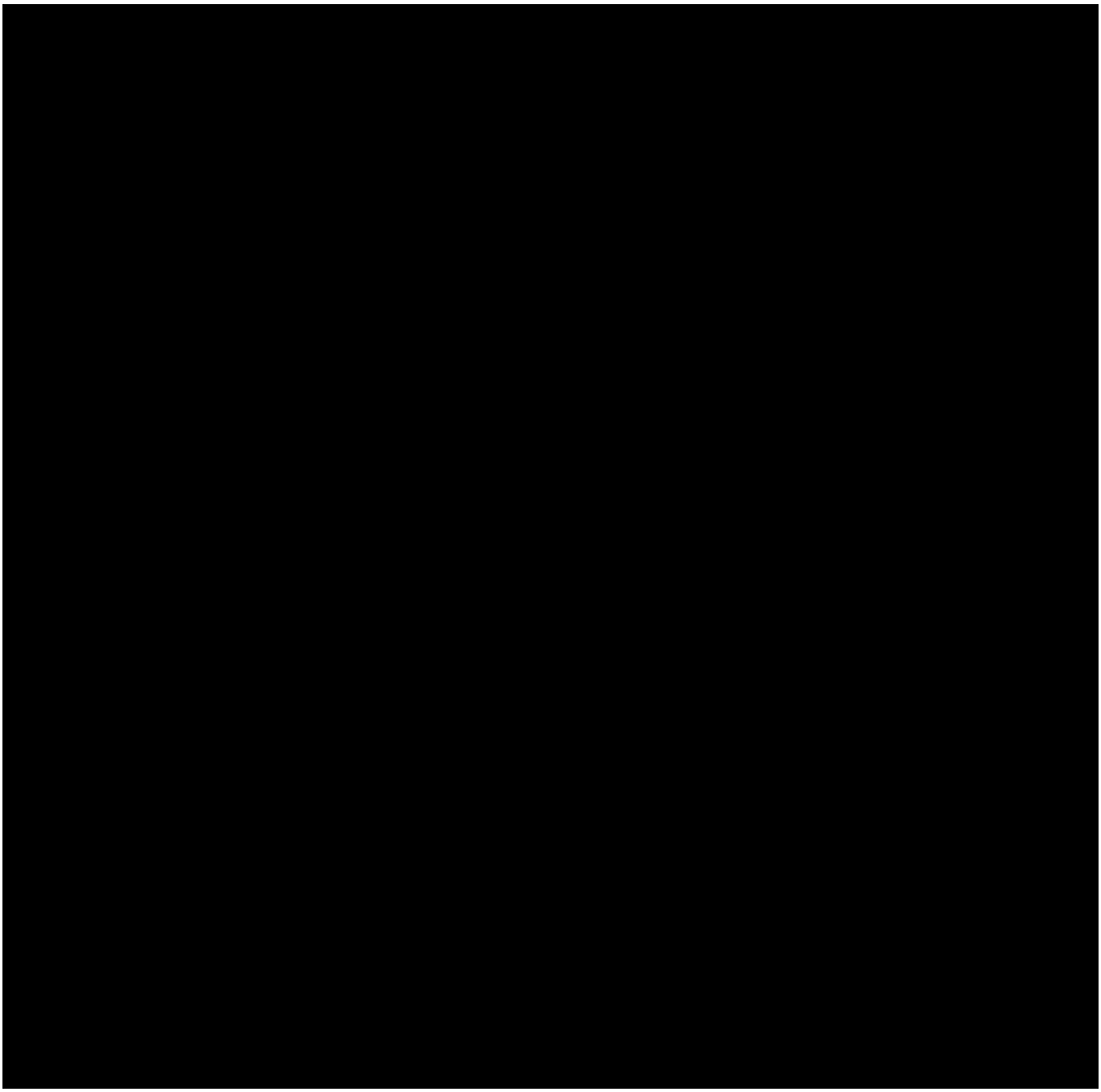
11. Robinson WH, Genovese MC, Moreland LW: Demyelinating and neurologic events reported in association with tumor necrosis factor alpha antagonism: By what mechanisms could tumor necrosis factor alpha antagonists improve rheumatoid arthritis but exacerbate multiple sclerosis? Arthritis Rheum 2001;44:1977-83.

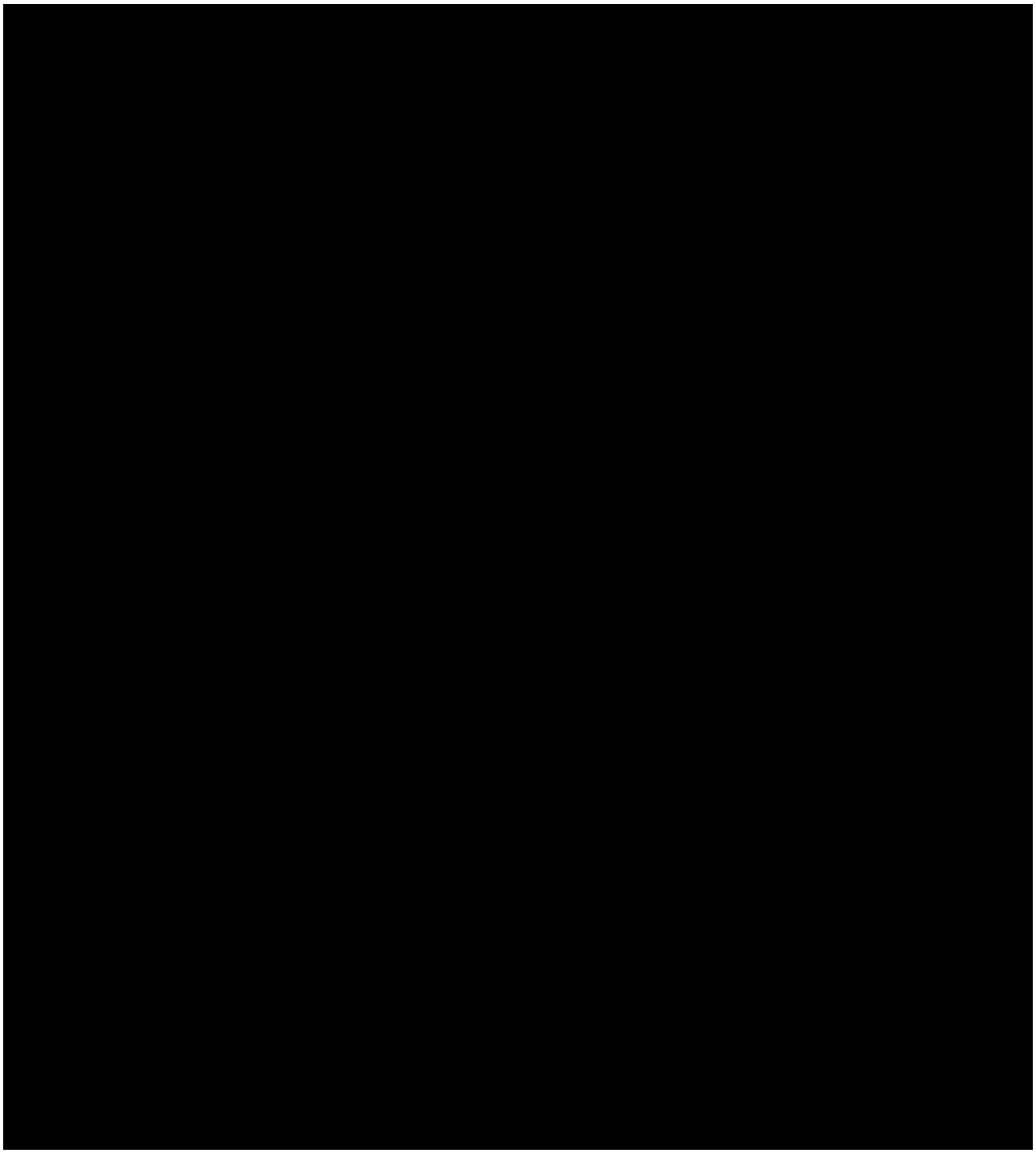
12. Saag KG, Teng GG, Patkar NM et al. American College of Rheumatology 2008 Recommendations for the use of nonbiologic and biologic disease modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59(6):762-84

27 APPENDICES

Appendix A ARA & ACR Criteria



Appendix B ACR Score



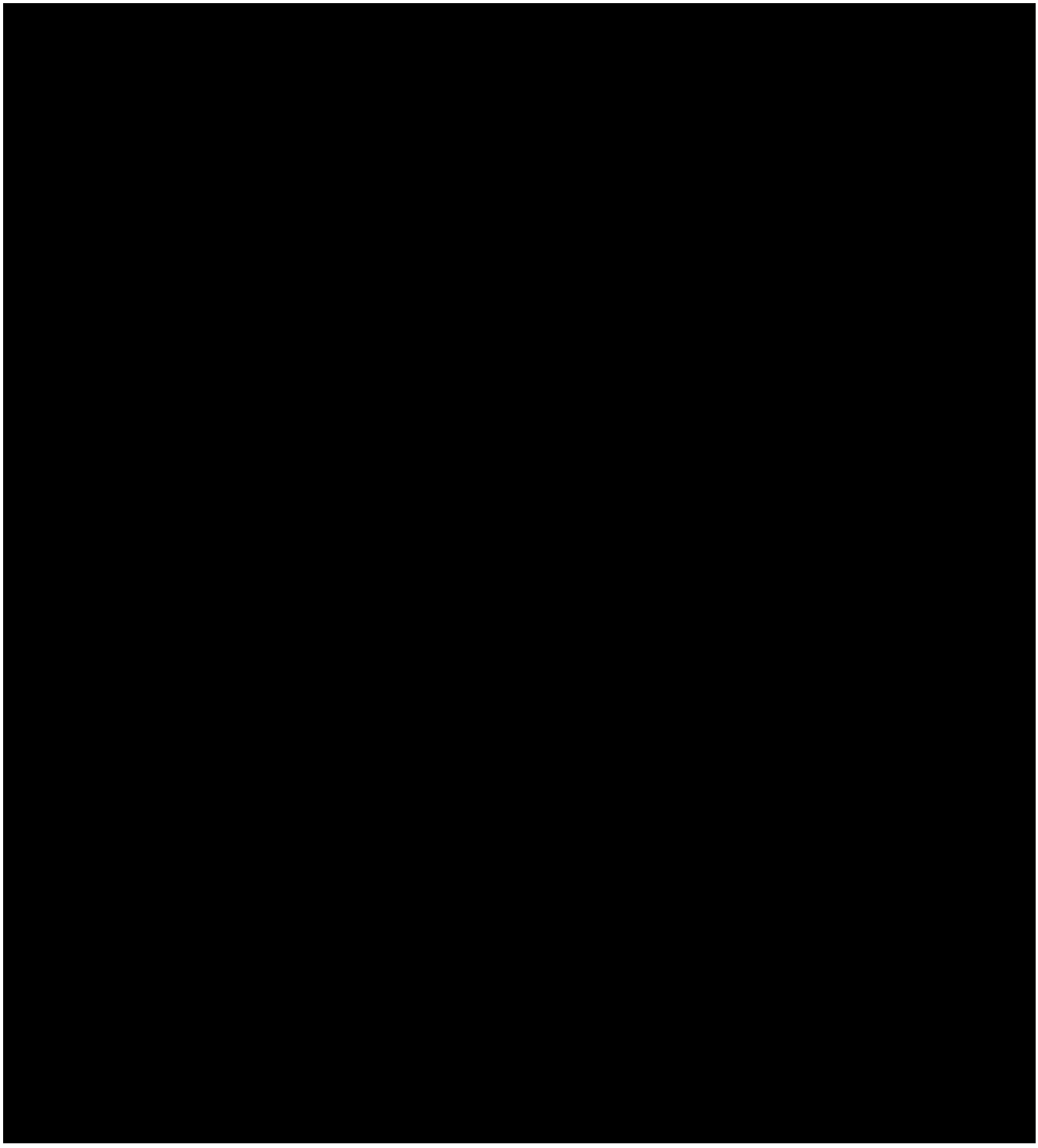
Appendix C Sharp Van Der Heijde Method

Appendix D Subject's Global Assessment of Disease Activity

Appendix E Subject's Assessment of Pain

Appendix F FACIT-Fatigue Scale

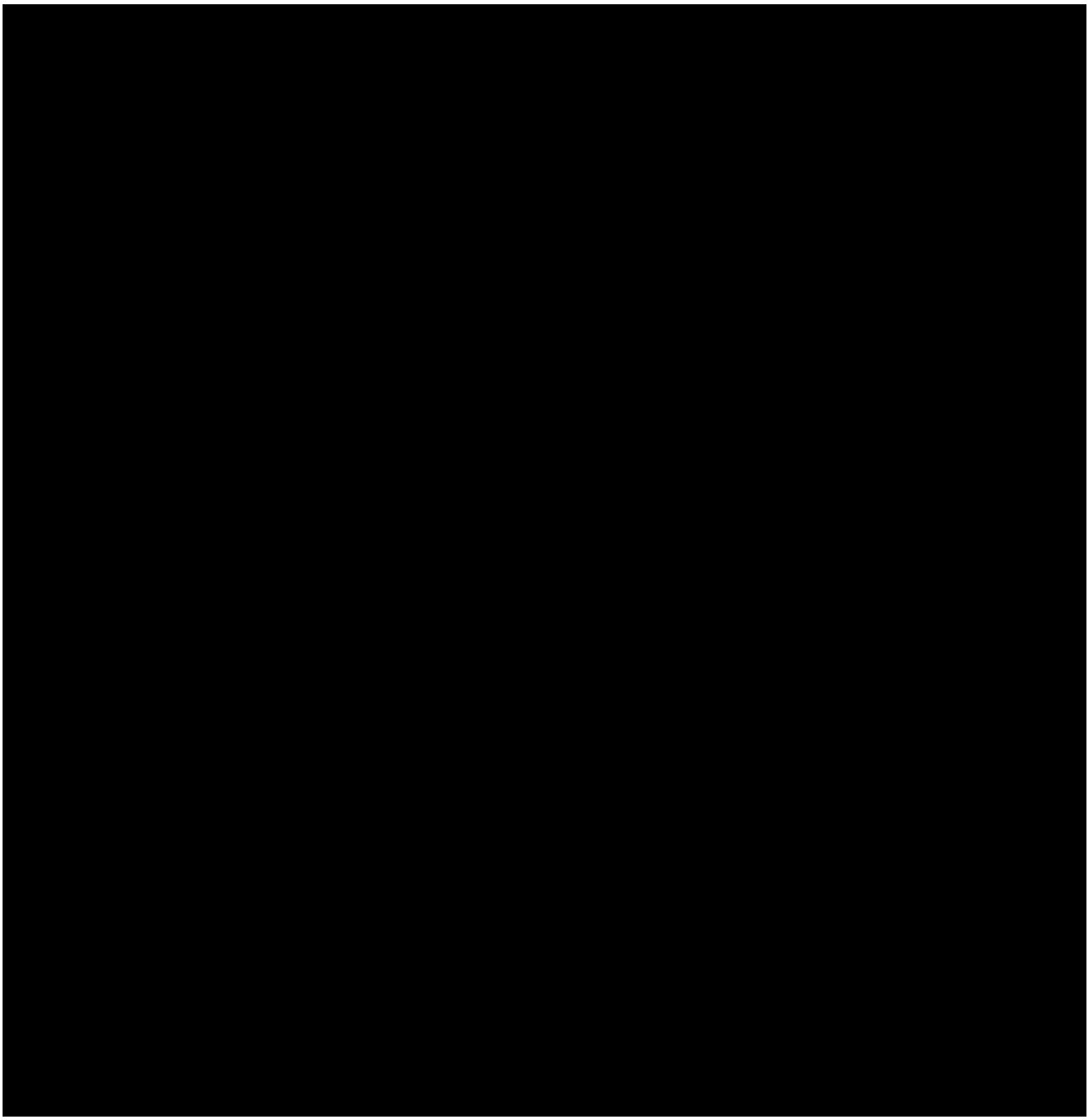
Appendix G WPAI Questionnaire



Appendix H Sleep questionnaire (VAS)

Appendix I SF-36 Health Survey

(SF-36v2 Standard, US Version 2.0)



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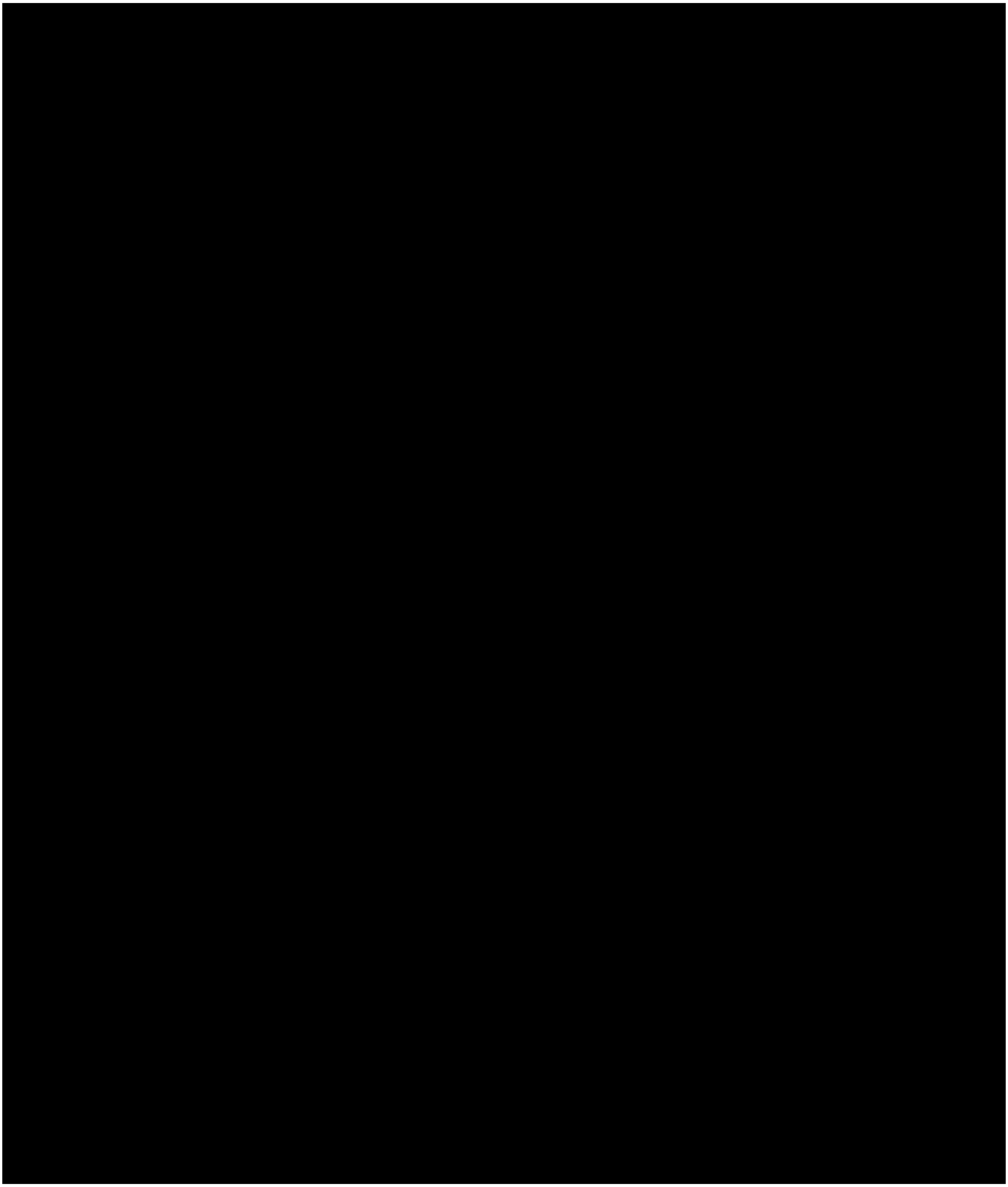

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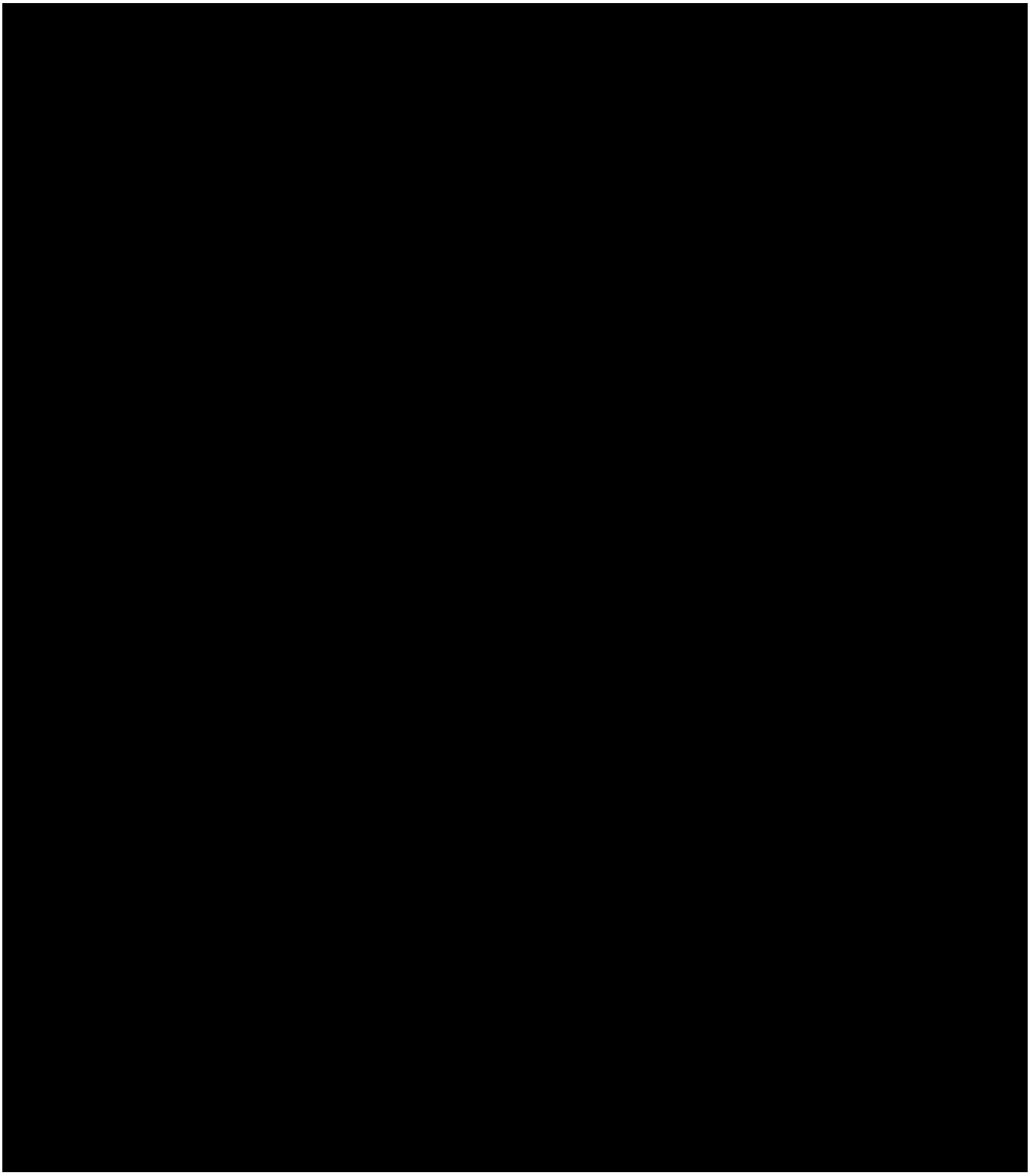
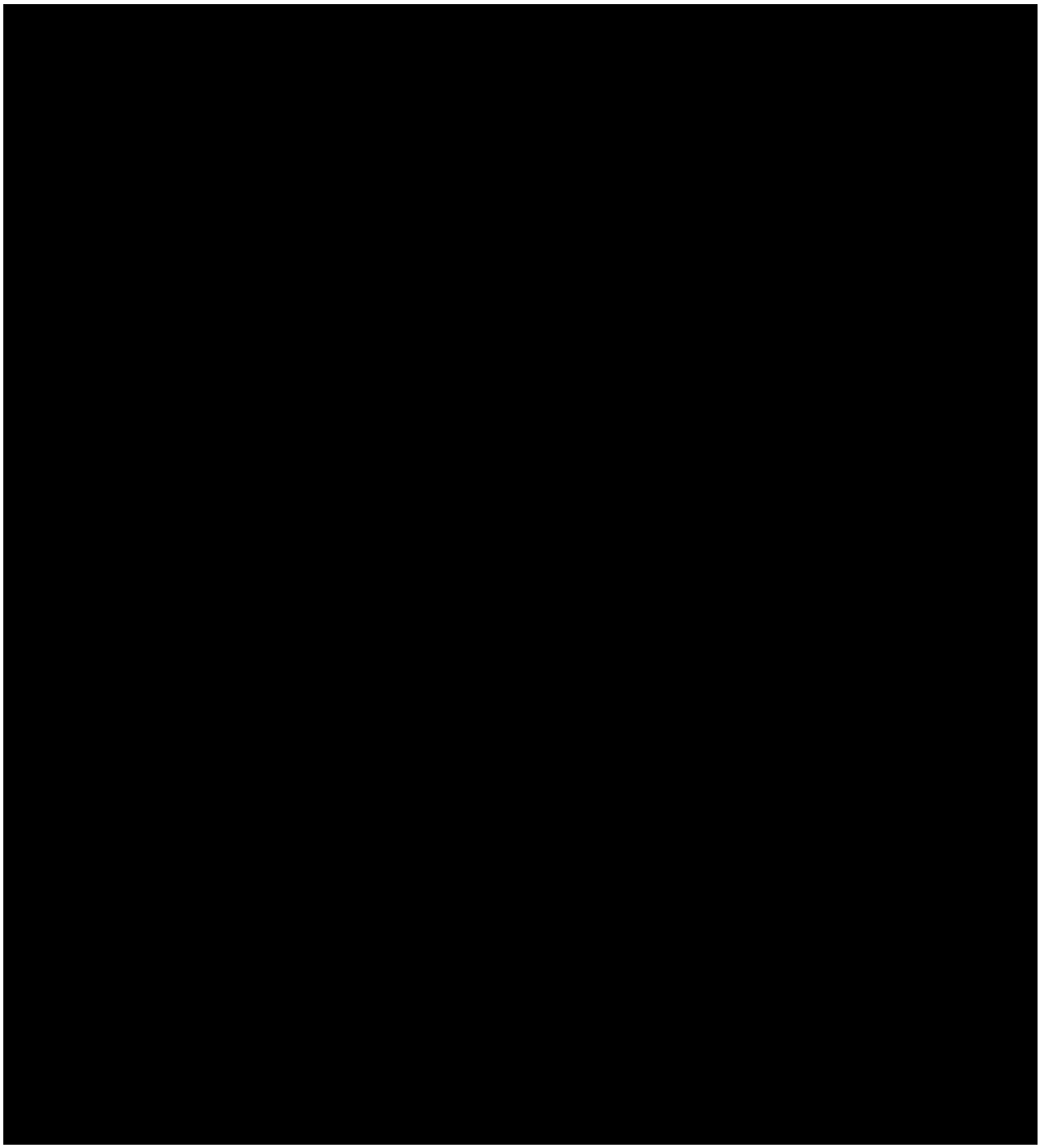
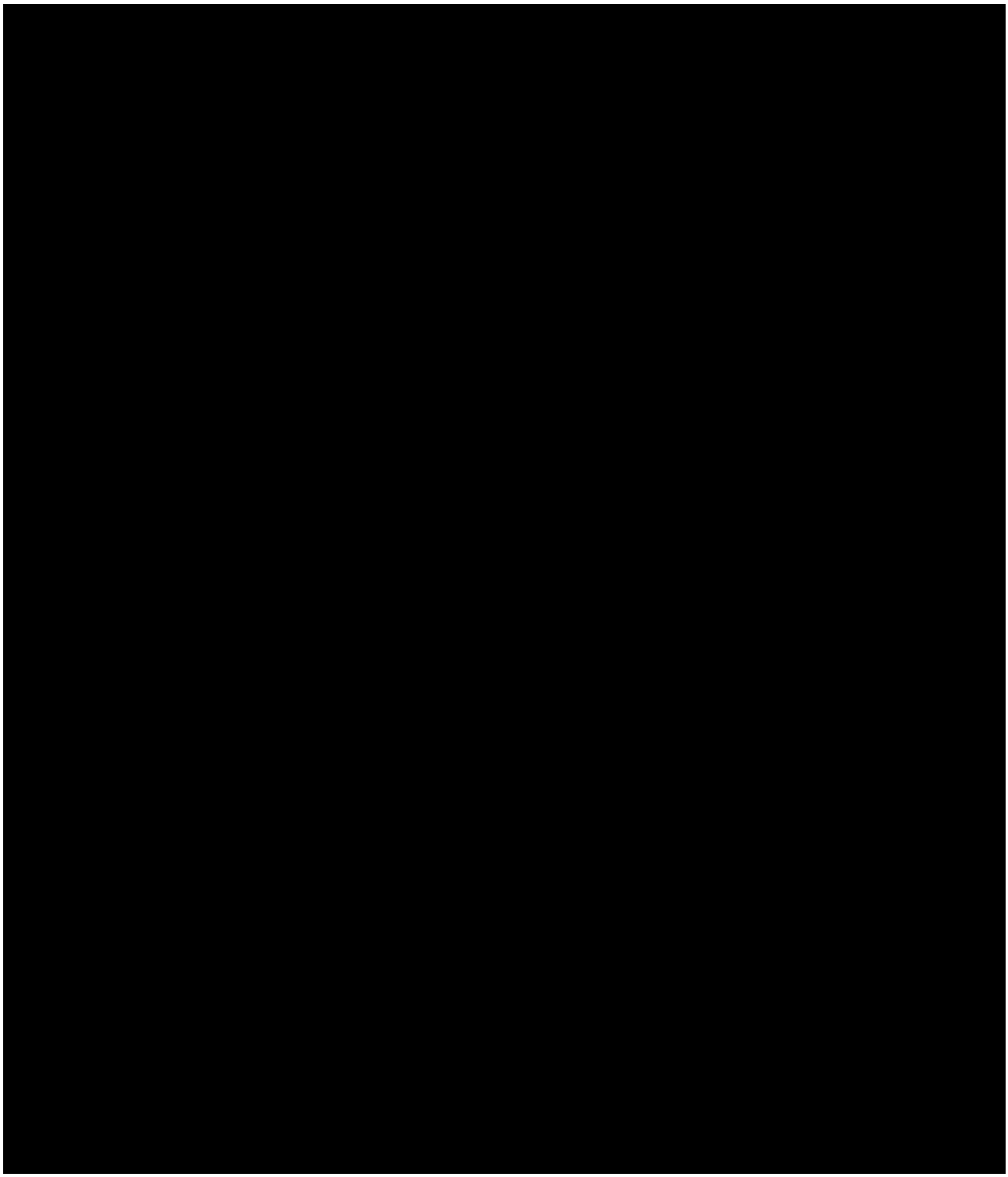


(SF-36v2 Standard, US Version 2.0)

(SF-36v2 Standard, US Version 2.0)

Appendix J HAQ-DI – Health Assessment Questionnaire

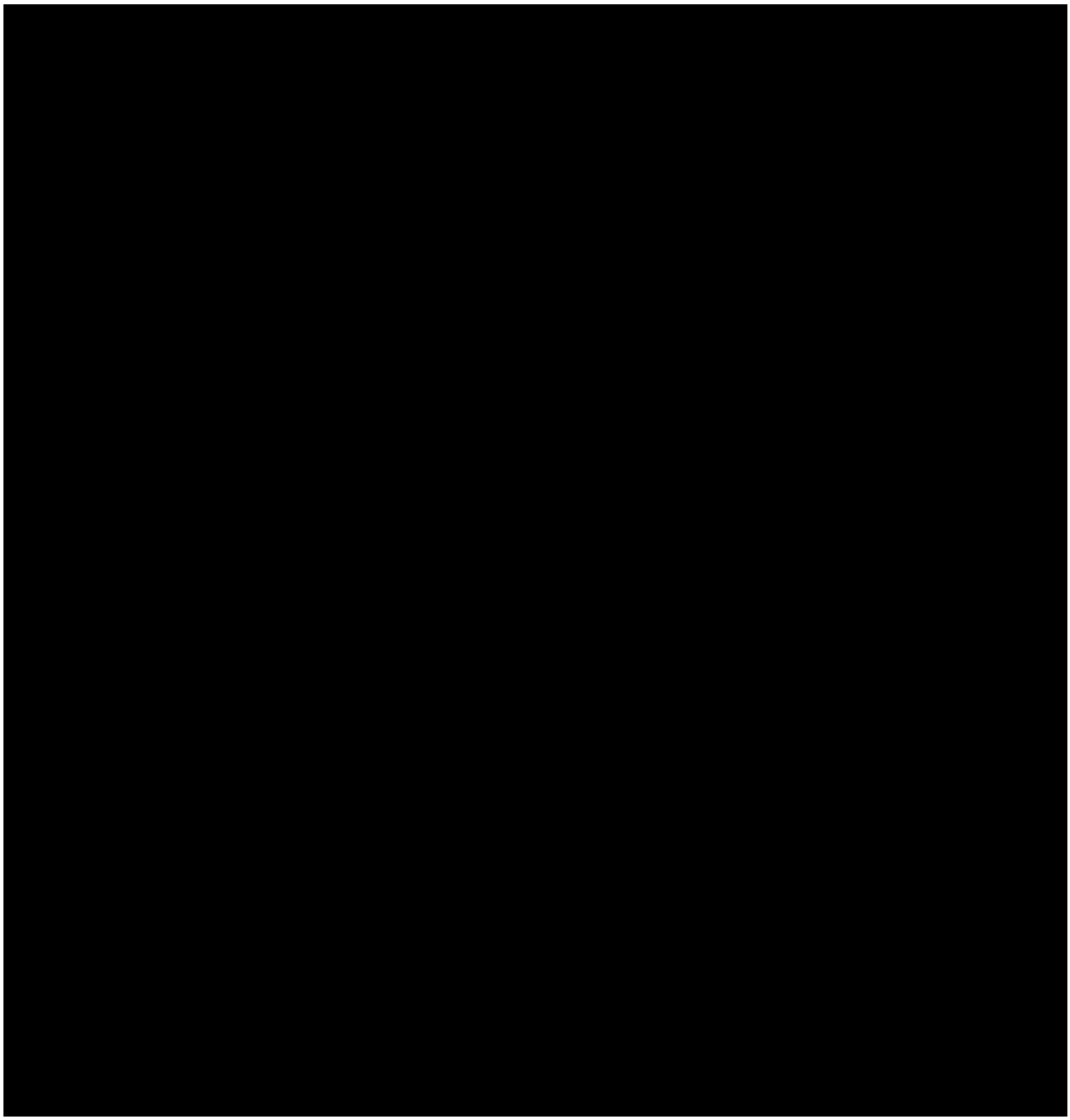


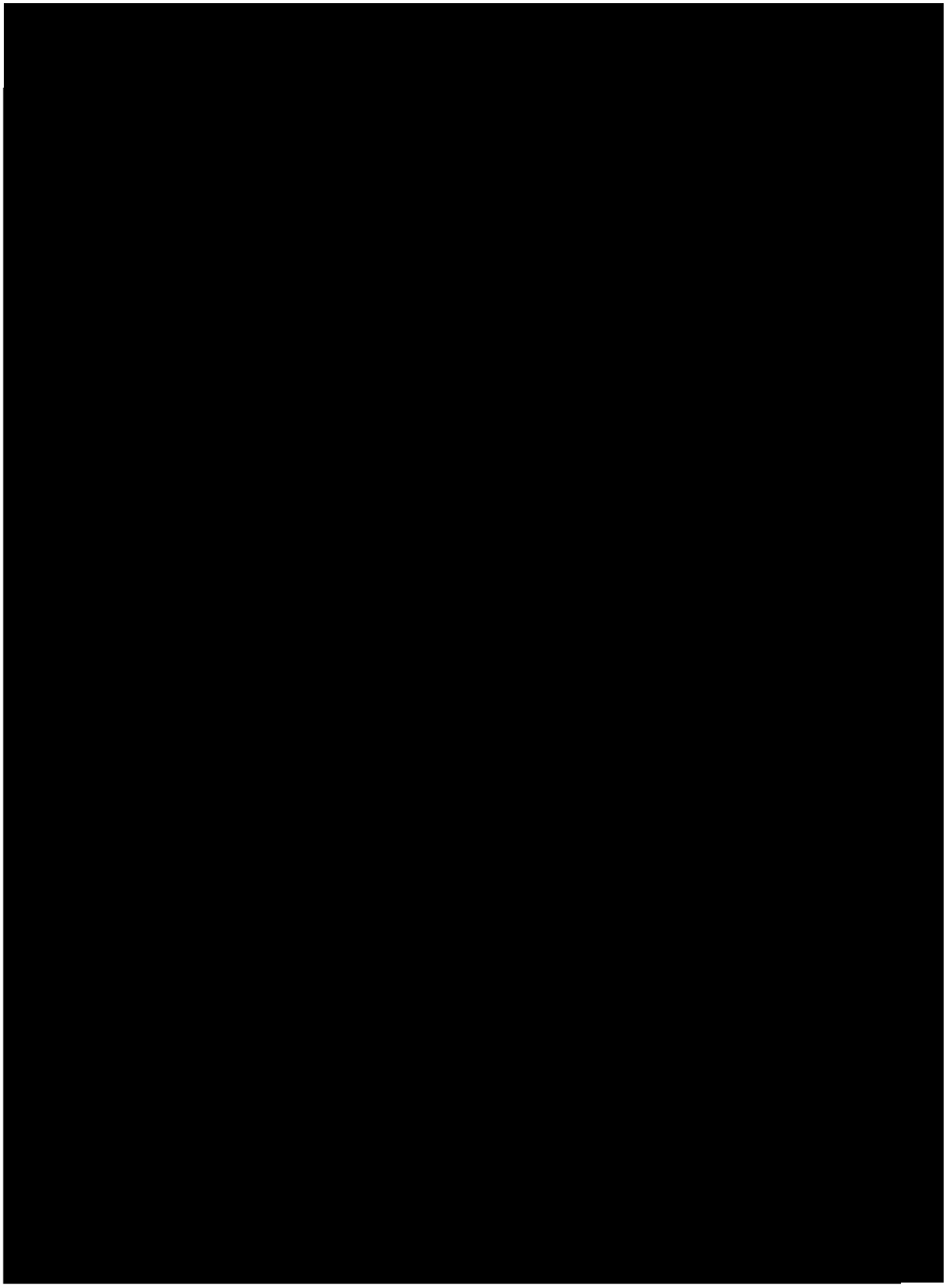


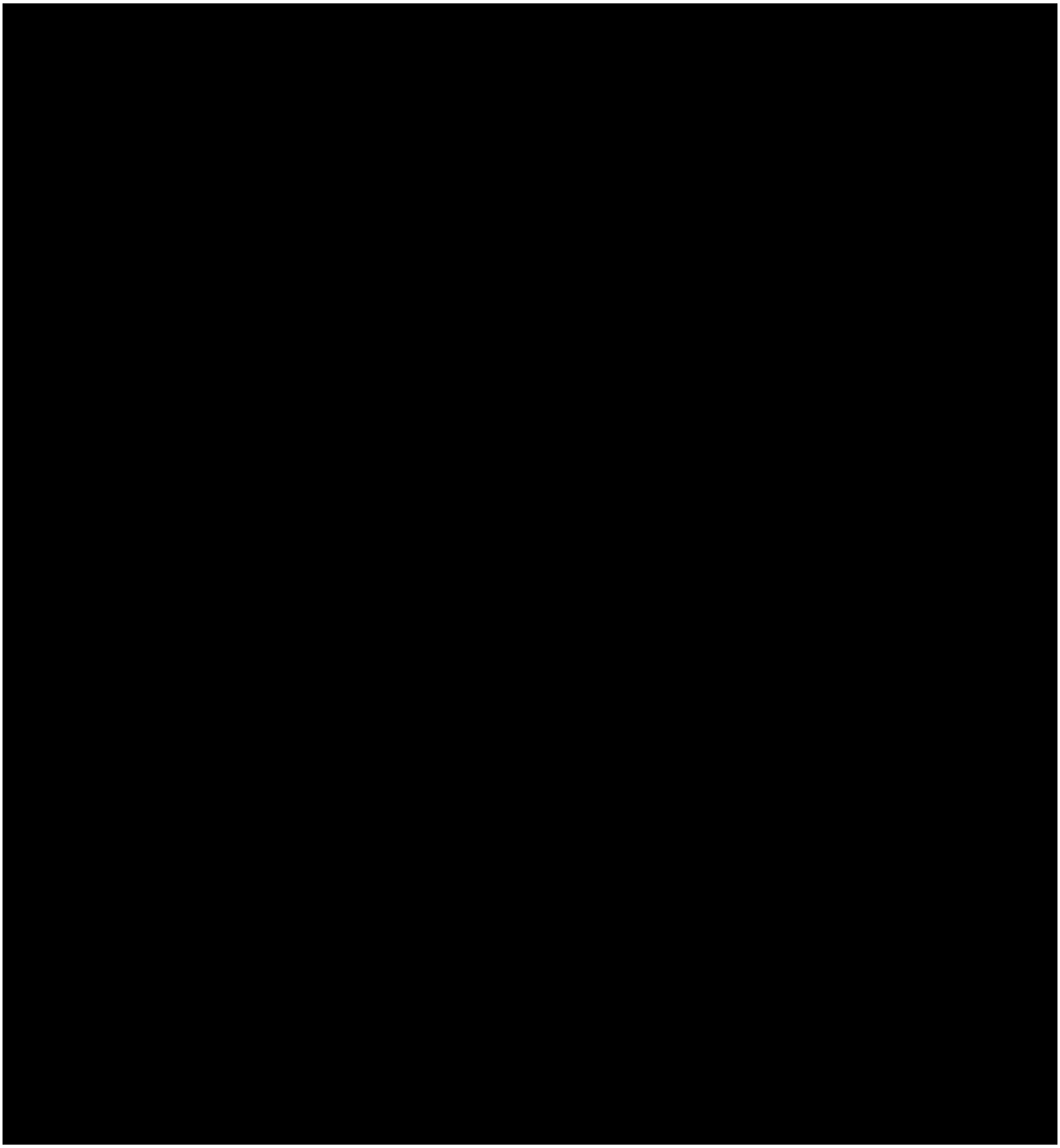
Appendix K Prohibited Live (Attenuated) Vaccine List

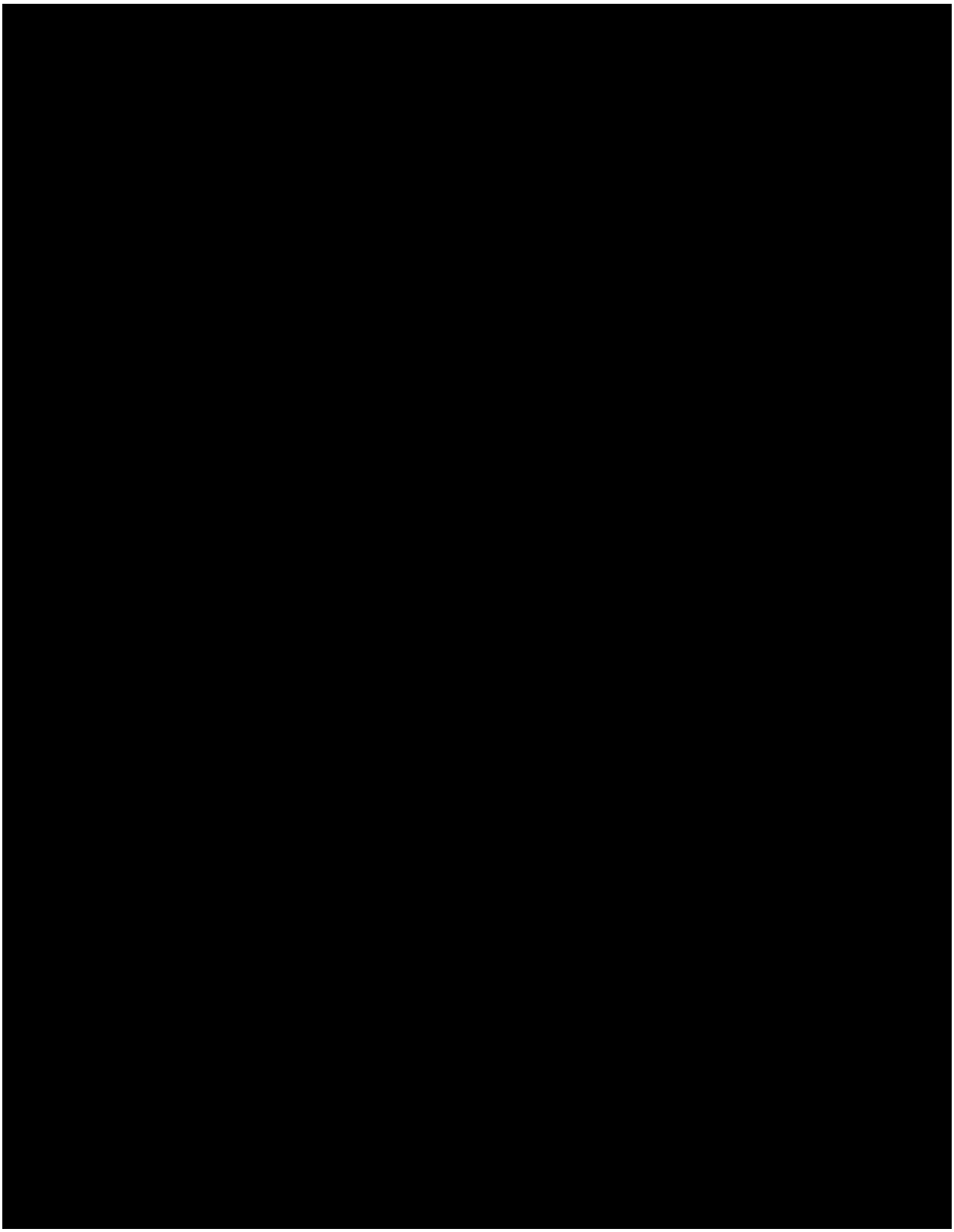
- Chickenpox (Varicella)
- Intranasal influenza
- Measles (Rubeola)
- Measles-mumps-rubella (MMR) combination
- Mumps
- Oral polio (Sabin)
- Oral typhoid
- Rubella
- Smallpox (Vaccinia)
- Herpes zoster
- Yellow fever
- BCG

Appendix L General Guidance for the follow-up of laboratory abnormalities by sanofi-aventis









Appendix M List of potential opportunistic infections

- Tuberculosis
- Aspergillosis
- Blastomyces dermatitiidis (endemic in the south-eastern and south-central states US, along Mississippi and Ohio Rivers)
- Candidiasis – systemic or extensive mucocutaneous cases
- Coccidioides immitis (endemic south-western US and Central and South America)
- Paracoccidiodomycosis
- Cryptococcus
- Cytomegalovirus
- Herpes Simplex (severe/disseminated)
- Herpes Zoster
- Histoplasmosis (pulmonary or disseminated; most common tropical areas Tennessee-Ohio-Mississippi river basins)
- Listeriosis
- Infection with mycobacterium avium and other non-tuberculosis mycobacteria
- Pneumocystis pneumonia (PCP)

This list is indicative and not exhaustive.

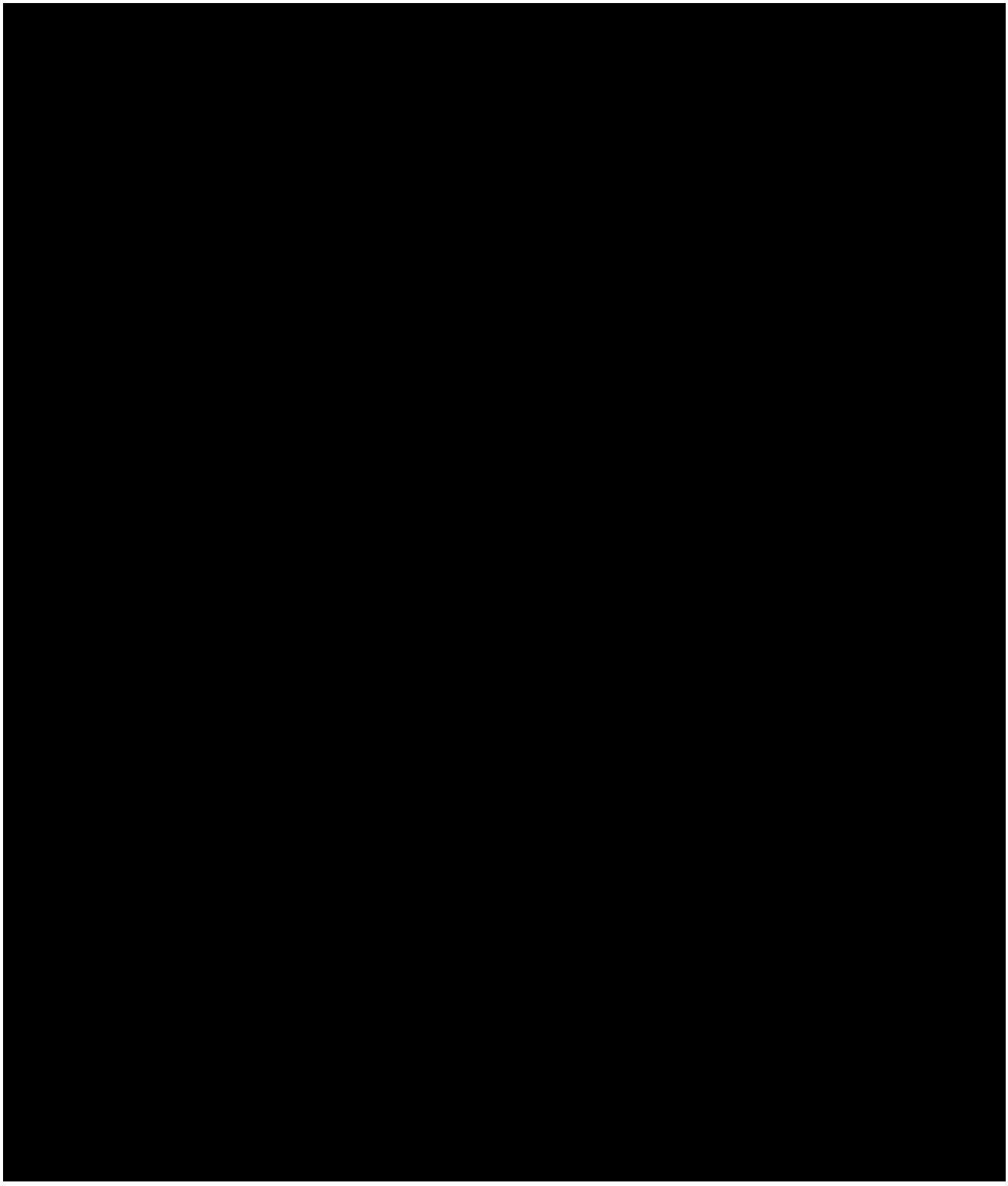
Appendix N DELETED

Appendix O Clinical criteria for diagnosing anaphylaxis

H.A. Sampson et al – J Allergy Clin Immunol, 2006; vol 117, n°2 : 391-7.

Appendix P DELETED

Appendix Q WPS-RA Questionnaire



Appendix R Abbreviated protocol of PFS-S sub-study

TITLE: A multi-center open-label sub-study of SARIL-RA-EXTEND to explore the usability of the sarilumab pre-filled syringe with safety system (PFS-S) in patients with active Rheumatoid Arthritis (RA)

COMPOUND: SARILUMAB (SAR153191)

STUDY NUMBER: LTS11210

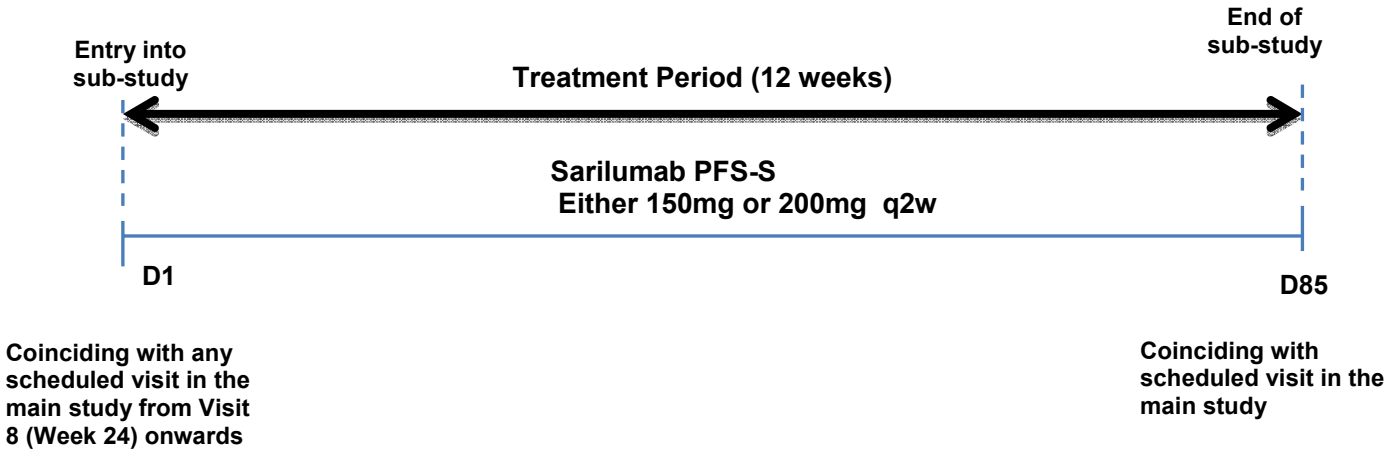
STUDY NAME: SARIL-RA-EXTEND SUB-STUDY

This abbreviated protocol of sub-study includes only components additional to the main study

Version Number:	1	EudraCT and/or IND Number(s)	2010-019262-86 / 100,632
Date:	31-Aug-2015	Total number of pages:	22

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

All assessments planned to be performed at the scheduled main study visit that coincides with the sub-study visit, are described in the main study flow charts. Below flowchart specifies only:

- those actions that are additional to the scheduled main study visit in LTS11210
- those actions that replace an action in the scheduled main study visit in LTS11210 (for example, study drug dispensing of the PFS-S IMP format, instead of the main study IMP in PFS)

	Sub-study assessments	
VISIT	V101	V102
DAY **Week**	D1 Wk0	D85 (+/- 3 days) Wk12
Eligibility	X	
Written Informed Consent	X	
IVRS call to start / end sub-study participation	X	X
Training on use of the PFS-S	X	
Dispense PFS-S[a]	X	
Dispense sub-study injection diary[b]	X	
Collect / review sub-study injection diary[b]		X
PTC reporting		X
AE related to a PTC reporting[c]		X
Serum Sarilumab (PK)[d]	X	X
ADA[d]	X	X

a PFS-S dispensing will replace the scheduled IMP dispensing at the main study visit
b Sub-Study Injection Diary dispensing and review will replace the dispensing and review of the main study Patient Diary in the scheduled main study visits
c Refer to Section 10.4.1 for instruction of reporting AE related to PTC
d If the sub-study visit coincides with a PK and ADA sampling time point in the main study, no additional samples are required for the sub-study

2 TABLE OF CONTENTS

Not applicable.

3 LIST OF ABBREVIATIONS

Only abbreviations related to the sub-study are listed here

AESI: Adverse Event of Special Interest
ALP: Alkaline Phosphatase
ALT: Alanine Aminotransferase
AST: Aspartate Aminotransferase
CV%: Coefficient of Variation
ECG: Electrocardiogram
FDD: failed drug deliveries
HDL: High Density Lipoprotein
IMP: investigational medicinal product
PFS-S: pre-filled syringe with safety system
PROs: Patient Reported Outcomes,
PT: Preferred Term, Prothrombin Time
PTC: product technical complaint
PTF: product technical failure
SD: Standard Deviation
SEM: Standard Error of the Mean
TB: Tuberculosis

4 INTRODUCTION AND RATIONALE

4.1 PRE-FILLED SYRINGE WITH SAFETY SYSTEM (PFS-S)

Sarilumab has been delivered via prefilled syringes (PFS) in most of the Phase 3 studies.

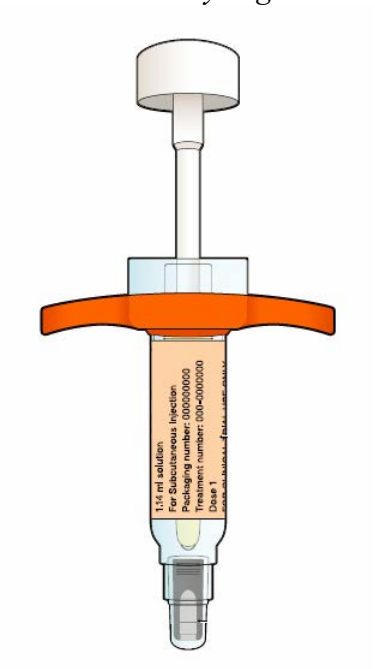
The pre-filled syringe with safety system (PFS-S) is a modified version of the prefilled syringe aimed at preventing needle stick injury by either the patient or by a caregiver (professional or non-professional) performing the administration. The "safety system" consists of a sharps injury prevention feature, which can be described as a sheath that automatically covers the needle once the injection is completed and thus prevents needle stick injury and re-use.

Compared to PFS, PFS-S also includes:

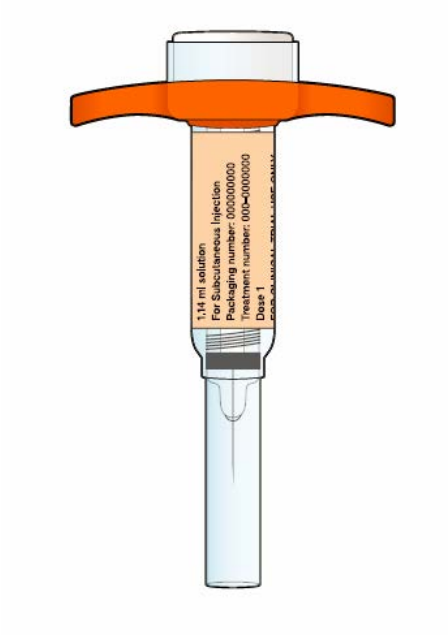
- a rigid needle shield that encloses the soft rubber needle shield covering the needle
- a finger flange with an ergonomic design and a large piston rod

The following figures show the unused and used PFS-S. At the end of the injection when the plunger rod has been pushed into the syringe as far as it will go, the needle safety shield is activated which can be seen as the syringe is pulled away from the skin.

Unused syringe



Used syringe with activated needle safety shield



4.2 SUB-STUDY RATIONALE

This sub-study is aimed to assess the usability of the PFS-S syringe when used by patients with moderate or severe RA, or their professional or non-professional healthcare providers in an unsupervised real-world situation. To mimic the real-world practice, the sub-study was designed to incorporate into the LTS11210 study without additional visits compare to scheduled visits in the main study.

The primary endpoint is the number of product technical failures (PTF), which is defined as any product technical complaint (PTC) that has a validated technical cause. A PTC is defined as any patient- or healthcare provider-reported complaint regarding the use of the PFS-S syringe and collected via the completion of the injection diary.

In addition, the safety information of sarilumab 150 mg q2w PFS-S and 200 mg q2w PFS-S will be collected throughout the sub-study period and trough concentrations of sarilumab will be measured at entry into the sub-study and at the end of the 12-week sub-study period.

5 STUDY OBJECTIVES

5.1 PRIMARY

To assess the usability of the sarilumab pre-filled syringe with safety system (PFS-S) when administered to patients with active Rheumatoid Arthritis (RA)

5.2 SECONDARY

To document the safety of sarilumab 150 mg q2w PFS-S and sarilumab 200 mg q2w PFS-S

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is a Phase 3, multicenter, worldwide, non-randomized, open-label, 1-arm, 12-week sub-study of the LTS11210/SARIL-RA-EXTEND study. The sub-study will only be performed in limited sites in selected countries.

Patients at participating sites who have been enrolled in the main study (LTS11210) for at least 24 weeks and are willing to participate in the sub-study will be enrolled in the sub-study. The entry into the sub-study (V101) will be at any scheduled visit in the main study from Visit 8 (Week 24) or after. Sarilumab 150 mg q2w PFS-S or sarilumab 200 mg q2w PFS-S will be used in the sub-study to replace the sarilumab 150 mg q2w PFS or 200mg q2w PFS used in the main study. At the entry into the sub-study (V101), the patients will be trained how to use the PFS-S, and the sub-study injection diary will be dispensed to replace the patient diary of the main study. All the procedures described in the sub-study are additional to the main study activities, unless specified to replace procedures in the main study.

The person performing each sub-study injection will respond to 3 questions related to PFS-S use on the injection diary (See Section 9.1) after each PFS-S injection. A “no” response to any question will be defined as a PTC. For any PTC, the Investigator will complete a PTC form and will send this PTC form together with the PFS-S that triggered this PTC back to the Sponsor according to a predefined process (Section 12). The patients should be instructed to keep any PFS-S associated with a PTC separately from other PFS-S, so it can be identified when returned to site at the end of sub-study.

For patients receiving sarilumab 200 mg q2w PFS-S the dose can be reduced any time during the sub-study duration if the main protocol defined criteria for dose reduction are fulfilled.

When the patients have completed the 12 weeks of the sub-study they will return to the clinic to complete Visit 102 in addition to the scheduled main study visit on that day. They will switch back to the main study and continue sarilumab PFS treatment.

If the patient chooses to end the participation in the sub-study during the sub-study duration but to continue in the main study the Visit V102 should still be completed.

If a patient discontinues Investigational Medicinal Product (IMP) permanently in LTS11210 during the sub-study, he/she should complete all procedures planned for V102 in the sub-study as well as the end of treatment (EOT) and post treatment follow-up visits in the main study (see flowchart in main study Section 1.2).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

Each patient will participate in the sub-study for a period of 12 weeks from the first sub-study visit (V101) to the final sub-study visit (V102). At the time of V101, eligible patients will start receiving sarilumab 150 mg q2w PFS-S or sarilumab 200 mg q2w PFS-S for 12 weeks as replacement of original sarilumab PFS in the main study and on top of the background disease modifying anti-rheumatic drugs (DMARDs) therapy, if any. There is no post-treatment follow-up specific to the PFS-S sub-study, as all patients will switch back to the main study at V102.

6.2.2 Determination of end of sub-study (all patients)

The last on-treatment sub-study visit for patients who complete the sub-study will occur at Day 85 (Visit 102). The sub-study will be considered completed when the last sub-study patient has completed V102.

6.3 INTERIM ANALYSIS

No interim analysis is planned.

6.4 STUDY COMMITTEES

Please refer to the main study protocol.

7 SELECTION OF PATIENTS

Approximately 120 patients active in the main study (LTS11210) are planned to be enrolled at selected sites in countries participating in the sub-study.

7.1 INCLUSION CRITERIA

I 01. Patients enrolled in the LTS11210 study who are receiving either sarilumab 200mg q2w PFS or sarilumab 150mg q2w PFS and who are able and willing to participate in this sub-study

I 02. Patients who have been enrolled in the main study for at least 24 weeks

I 03. Patients must sign a sub-study written informed consent prior to any sub-study related procedure

7.2 EXCLUSION CRITERIA

There are no additional exclusion criteria to those defined in LTS11210.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Investigational Medicinal Product
Sarilumab, anti-IL-6R mAb (anti-interleukin 6 receptor monoclonal antibody)

Pharmaceutical form
1 mL long glass prefilled syringes with a needle safety shield (PFS-S) filled to a nominal injection volume of 1.14 mL with drug product at 131.6 mg/mL (150 mg) or 175 mg/mL (200 mg)

Dose per administration

- Single-use administration of sarilumab by PFS-S
- Dose of either 150 mg or 200 mg q2w

NOTE: Patients should continue to receive the same sarilumab dose as they have received in the main study, unless they fulfill main protocol defined criteria for dose reduction.

Route and method of administration
The route and administration method of sarilumab PFS-S used in the sub-study are same as sarilumab PFS used in the main study.

Each sub-study injection will be performed by the patient, or their caregiver. In exceptional circumstances (such as the 1st administration using PFS-S) the injection may be performed by the site staff. The patient or their caregiver will be trained on performing the injection with the PFS-S using a patient user instruction specific to the use of the PFS-S and a training PFS-S filled with sucrose together with an injection pad. This training must be documented in the patient's study file.

Duration of administration of PFS-S
12 weeks (6 injections)

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

NIMP received in the sub-study corresponds to NIMP received in the main study.

8.3 BLINDING PROCEDURES

Not applicable. This is an open-label study.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

This is a 1-arm open-label sub-study, no randomization will be performed for the study.

At the sub-study entry (V101/D1), after the patient has given informed consent and the patient's eligibility has been confirmed, the site staff will contact the IVRS/IWRS in order to enroll the patient into the sub-study and to allocate the sub-study treatment kits. Either sarilumab 150 mg q2w PFS-S or sarilumab 200 mg q2w PFS-S will be allocated to each patient. The allocated dose will be the same as in the main study except if conditions for dose reduction are met.

The sub-study patients will continue to use the same patient number assigned during enrollment into the main study, which consists of 9 digits (3 digits indicating the country, 3 digits indicating the site and 3 digits indicating the patient)

8.5 PACKAGING AND LABELING

The IMP (sarilumab in PFS-S) will be provided in a patient treatment kit box. The kit will be labeled in accordance with the local regulatory specifications and requirements, along with content information, dosing instructions, and precautionary statement ("for clinical use only"). A sub-study treatment kit has specific labeling that distinguishes syringes in a treatment kit. They are labeled "Dose 1" and "Dose 2".

Packaging is in accordance with the administration schedule. The number of treatment kits allocated to the patient will provide sufficient medication until the next clinic visit. Additional treatment kits, to provide medication to patients under circumstances, such as a damaged kit, will be allocated by IVRS/IWRS when a "replacement treatment call" is made to IVRS/IWRS.

8.6 STORAGE CONDITIONS AND SHELF LIFE

The storage conditions and shelf life of sarilumab PFS-S used in the sub-study are the same as sarilumab PFS used in the main study.

8.7 RESPONSIBILITIES

Site personnel responsibilities in the sub-study are the same as in the main study.

8.7.1 Treatment accountability and compliance

The completed injection diary should be returned by the patient at the end of the sub-study (V102/D85).

All PFS-S medication treatment kits (with all used or unused PFS-S) must be returned by the patient at the end of the sub-study (V102/D85).

The study coordinator will track treatment accountability/compliance of PFS-S by comparing the information recorded in the patient diary with the number of returned treatment boxes and used/unused PFS-S and fill in the appropriate page of the patient treatment log.

The monitor in charge of the study will then check the data entered on the e-CRF IMP administration page by comparing them with the IMP that has been retrieved and the patient treatment log.

8.7.2 Return and/or destruction of treatments

All used and unused PFS-S will be collected by the study site at V102/D85. All used PFS-Ss for which a PTC was reported will be returned to the Sponsor.

At selected sites, used PFS-S which functioned normally with no PTC will be returned to the Sponsor as well.

Used PFS-S with complaints regarding labeling, packaging or a cosmetic defect of the PFS-S, will not be further investigated as a part of the sub-study.

A detailed treatment log of the returned PFS-S returned to the sponsor will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

8.8 CONCOMITANT MEDICATION

Prohibited and permitted concomitant medication is defined in the main study protocol.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

The primary endpoint is the number of validated PFS-S-associated PTFs. A PTF is defined as any PTC related to the use of the PFS-S which has a validated technical cause. A PTC is defined as any patient- or healthcare provider-reported complaint regarding the use of the PFS-S syringe and collected via the completion of the injection diary.

The injection diary will include specific questions about PTCs. The person performing each sub-study injection will record the answers to these questions in the diary each time he/she performs an injection with a PFS-S.

The questions include:

1. Were you able to remove the cap?

a) Yes

b) No

i If no, please describe / explain:

2. Was the needle safety system activated?

a) Yes

b) No

i If no, please describe / explain:

3. Did the safety system entirely cover the needle?

a) Yes

b) No

i If no, please describe / explain:

At Visit 102, the Investigator will review the diary, confirm with the patient whether there were any problems associated with the use of PFS-S either during drug administration or otherwise, and record the responses in the e-CRF.

If the answer is “no” to any of the questions stated in the diary, the patients will be asked to provide further details of the complaint and a PTC form will be completed by the investigator. The PTC form and the PFS-S associated with PTC will be sent to the Sponsor following the process defined in Section 12. The sponsor will validate or invalidate the occurrence of a PTF. If the PTF is ruled out the event is considered as a failed drug delivery (FDD) and is defined as patient’s failure to administer the full dose at a given attempt.

In addition, another question will be asked in the diary to confirm whether the person who performed the injection was trained:

4. Was the person who performed the injection the person who was trained by the site staff?

a) Yes

b) No

9.2 SECONDARY ENDPOINTS

9.2.1 Device related endpoints

- Number of PFS-S-associated product technical complaints (PTCs).
- Number and percentage of patients with PTFs
- Number and percentage of patients with PTCs
- Number and percentage of patients with FDDs

9.2.2 Safety endpoints

- Adverse events related to PTCs

Note: adverse events, laboratory values, vital signs, and electrocardiograms (ECG), assessed as part of the main LTS11210 study will not be described for the sub-study. If any adverse event reported during the sub-study is considered linked to a PTC by the investigator the potential link with the PTC should be specified in AE/SAE verbatim. If any laboratory or ECG abnormality or vital signs finding reported during the sub-study is considered clinically significant and linked to a PTC by the investigator an adverse event needs to be reported and the potential link with the PTC should be specified in AE/SAE verbatim. In addition a PTC of the PFS-S must be reported to the sponsor on a PTC form.

9.2.3 EXPLORATORY ENDPOINT OF pk

- Sarilumab C_{trough} at Day 1 and Day 85

9.2.4 PHARMACOKINETICS AND IMMUNOGENICITY

9.2.4.1 Sampling time

Pre-dose serum samples will be collected for determination of serum concentration of sarilumab and ADA at Visit V101 (D1) and at Visit V102 (D85). See study flow chart (Section 1.2).

Serum trough concentrations of functional sarilumab will be evaluated in patients on stable dose of sarilumab at V101 (D1) before using the PFS-S and at Visit V102 (D85) after 12 weeks administration of sarilumab using the PFS-S in the sub-study. Patients are considered to be on stable dose of sarilumab at V101 (D1) if they received the same dose of sarilumab without treatment interruption for at least 24 weeks in LTS11210 prior to V101.

9.2.4.2 Sample handling procedure

Sample handling procedures and bioanalytical method are same as in main study.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

All the procedures performed in the sub-study are in addition to those planned in the main study unless sub-study procedures replace the main study procedures.

10.1.1 Visit 101: Entry of sub-study / Day 1

A sub-study specific written informed consent form must be signed by the patient prior to any sub-study procedure being performed.

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

- Assess eligibility by review of inclusion criteria.
- Before sarilumab administration, obtain blood sample for PK (serum sarilumab) and anti-sarilumab antibodies assessment. If the sub-study visit coincides with a PK and ADA sampling time point in the main study, no samples are required to be obtained for the sub-study.
- Access IVRS/IWRS to enroll patient into the sub-study and to allocate sub-study IMP. NOTE: this replaces the scheduled resupply IVRS/IWRS transaction for the main scheduled study visit.
- Dispense sarilumab PFS-S.
- Dispense sub-study injection diary, provide instructions for use, and remind the patient to complete the diary after each injection and to bring the completed diary back to the site at next visit.
- Provide training on injection using a patient user instruction specific to the use of the PFS-S and a PFS-S prefilled with sucrose together with a pad. Allow the patient or the caregiver to inject into the training pad under observation, provide feedback on technique. This training must be documented in the patient's study file.
- The first dose of IMP will be administered by the patient or caregiver or study doctor/nurse at the study site and an appropriate record will be made in the source data by the person who performed the injection using the injection diary.

10.1.2 Visit 102: End of sub-study / Day 85

- Check compliance to the IMP and collect PFS-S medication kits and syringes (used and unused).
- Collect injection diary and review for content and completeness.
- Report diary feedback on each injection into the e-CRF.
- Collect and assess any PTC using the injection diary. The Investigator will ask the patient whether there were any problems associated with the PFS-S – either during drug administration or otherwise and will obtain more details as appropriate.

- Inquire about and record any adverse events/SAEs related to PTC.
- Prior to the IMP administration (sarilumab in PFS), obtain blood sample for sub-study PK (serum sarilumab) and anti-sarilumab antibodies assessment. If the sub-study visit coincides with a PK and ADA sampling time point in the main study, no samples are required to be obtained for the sub-study.
- Access IVRS/IWRS to register the end of sub-study and to obtain the next scheduled IMP (sarilumab in PFS) if the patient returns to the main study.

10.2 DEFINITION OF SOURCE DATA

Besides source data defined in the main study, the injection diary in sub-study is also considered as source data.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION DURING THE SUB-STUDY AND OF PATIENT STUDY DISCONTINUATION

Please refer to the main study as regards handling of patients at the time of temporary or permanent treatment discontinuation.

If the patient chooses to end the participation in the sub-study but to continue in the main study they should complete the Visit V102.

If a patient discontinues the Investigational Medicinal Product (IMP) permanently in LTS11210 during the sub-study, he/she should complete all procedures planned for V102 in the sub-study as well as the end of treatment (EOT) and post treatment follow-up visits in the main study (see flowchart in main study Section 1.2).

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Instructions for reporting PTC and adverse events related to PTC

PTCs may or may not be associated with an adverse event. Any PTC of the PFS-S, whether or not associated with an adverse event, must be reported to the sponsor on a PTC form.

If a PTC is suspected of being associated with the occurrence of an adverse event, the Investigator must document the adverse event on an adverse event page in the e-CRF, in addition to completing the PTC form. The potential link of the adverse event with the PTC must be specified in AE verbatim.

If a PTC is suspected of being associated with the occurrence of an SAE, the SAE must be reported in accordance with the SAE reporting procedures and the Investigator must specify the potential link with the PTC in SAE verbatim.

Please refer to the related section in the main study for general safety instructions.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size of this sub-study is based on empirical consideration. No formal sample size calculation is performed but an estimate of 120 patients included in this sub-study with up to 6 injections per patient will provide approximately 680 injections to evaluate PTF during the 12 weeks of the study assuming 5% of drop-out rate.

11.2 DISPOSITION OF PATIENTS

Enrolled patients are defined as any patient who met the inclusion criteria and none of the exclusion criteria, and signed the informed consent.

11.3 ANALYSIS POPULATIONS

The safety population will consist of all enrolled patients who receive at least 1 dose or part of a dose of IMP administered via PFS-S during this sub-study.

Safety analyses will be performed on the safety population. Patient data will be analyzed according to the treatment actually received (200mg q2w PFS-S, 150mg q2w PFS-S, dose reduction).

The PK population will consist of all enrolled patients who receive at least 1 dose of the IMP and at least one non-missing serum concentration value.

11.4 STATISTICAL METHODS

The phrase ‘treatment group’ used throughout this section refers to the following device/dose groups (200mg q2w PFS-S, 150mg q2w PFS-S, 200mg q2w PFS-S to 150mg q2w PFS-S). The baseline value is defined as original baseline in initial studies.

11.4.1 Extent of study treatment exposure and compliance

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

The duration of IMP exposure is defined as: last dose date – first dose date at D1 + 14 days (regardless of unplanned intermittent discontinuations). The duration of exposure to the IMP will be summarized for each treatment group by using descriptive statistics such as mean, SD, median, minimum, and maximum.

Treatment compliance to the IMP is defined as the actual number of doses received compared to the scheduled number of doses during the treatment period. It is calculated according to the following formula:

$$\frac{100 \times \text{total number of doses administered}}{\text{nominal number of doses for the duration of exposure}}$$

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

Treatment compliance during the treatment period will be summarized descriptively (N, mean, standard deviation, median, minimum, and maximum). The percentage of patients with compliance <80% will be summarized.

11.4.2 Analyses of endpoints

11.4.2.1 Analysis of primary endpoint(s)

Data will be described for the 12 weeks of this sub-study using the safety population. The primary analysis variable is the number of validated PFS-S-associated PTFs during the sub-study. The primary analysis will be performed using descriptive statistics.

11.4.2.2 Analyses of secondary and exploratory endpoints

Descriptive statistics will be used for continuous variables; discrete variables will be described using counts and proportions. Data will be presented by treatment dose group.

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

For PK parameters C_{trough}, estimates and 90% CIs for the ratio of geometric means (Day 85 versus Day 1) will be provided using a linear fixed effects model on the log-transformed data. Serum trough concentrations of functional sarilumab will be evaluated in patients on stable dose of sarilumab at V101 (D1) before using the PFS-S. Patients are considered to be on stable dose of sarilumab at V101 (D1) if they receive the same dose of sarilumab without treatment interruption for at least 24 weeks in LTS11210 prior to V101. Patients changing dose during the 12 week sub-study will be excluded from the C_{trough} analyses.

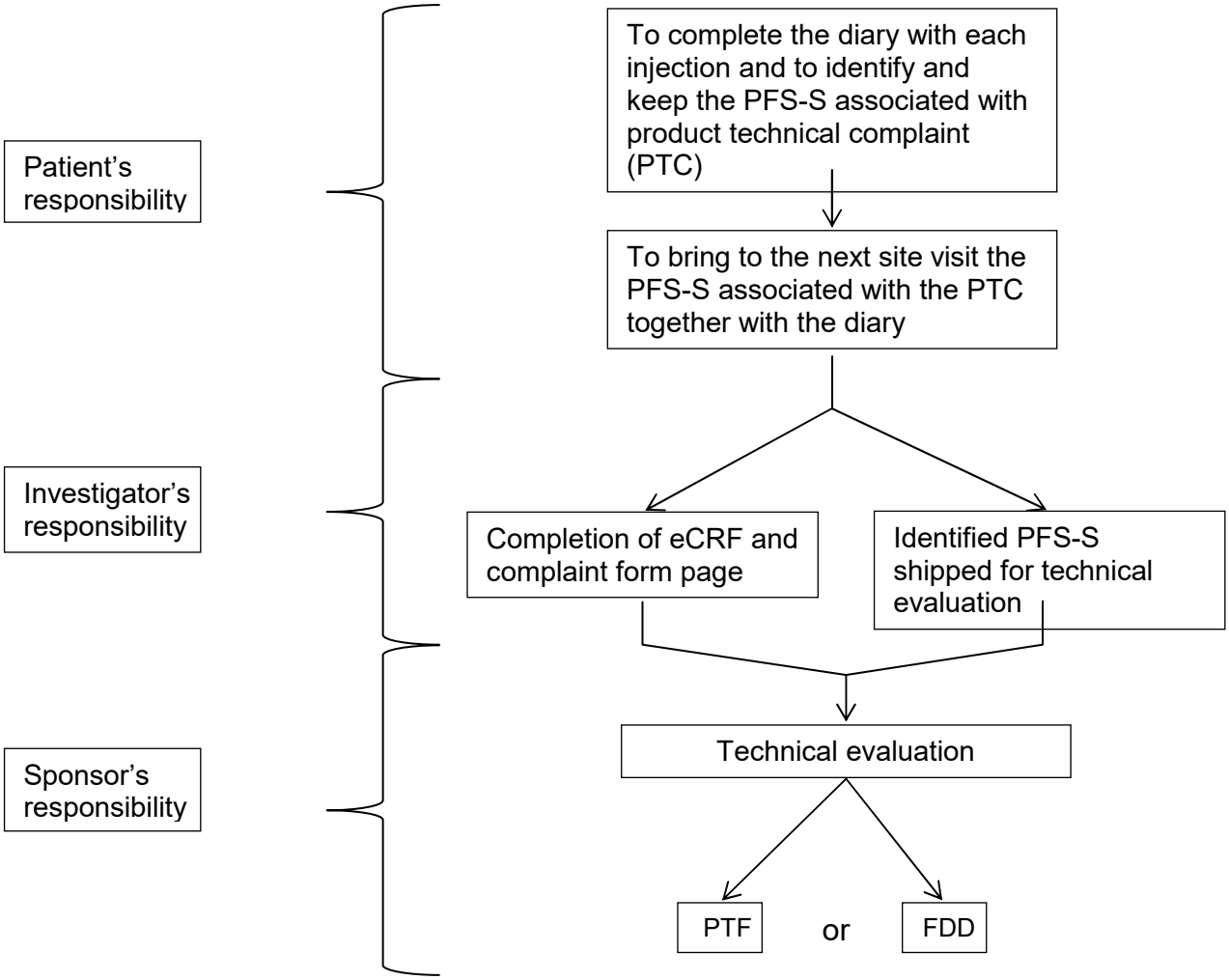
11.4.2.3 Multiplicity considerations

Not applicable

11.5 INTERIM ANALYSIS

No interim analysis is planned.

12 HANDLING PROCESS FOR PRODUCT TECHNICAL COMPLAINT REPORTING



PFS-S = pre-filled syringe with safety system; PTC= product technical complaint; PTF = product technical failure; FDD = failed drug delivery

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]		