AMENDED CLINICAL TRIAL PROTOCOL 03

COMPOUND: Sarilumab/SAR153191

An Open-label, Sequential, Ascending, Repeated Dose-finding Study of Sarilumab, Administered with Subcutaneous (SC) Injection, in Children and Adolescents, Aged 2 to 17 Years, with Polyarticular-course Juvenile Idiopathic Arthritis (pcJIA) Followed by an Extension Phase

STUDY NUMBER: DRI13925

STUDY NAME: SKYPP

VERSION DATE/STATUS: 12-Sep-2019 / Approved

Version Number:	1	EudraCT: IND Number(s): WHO universal trial number:	2015-003999-79 100632 U1111-1177-3487
Date:	12-Sep-2019	Total number of pages:	177

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

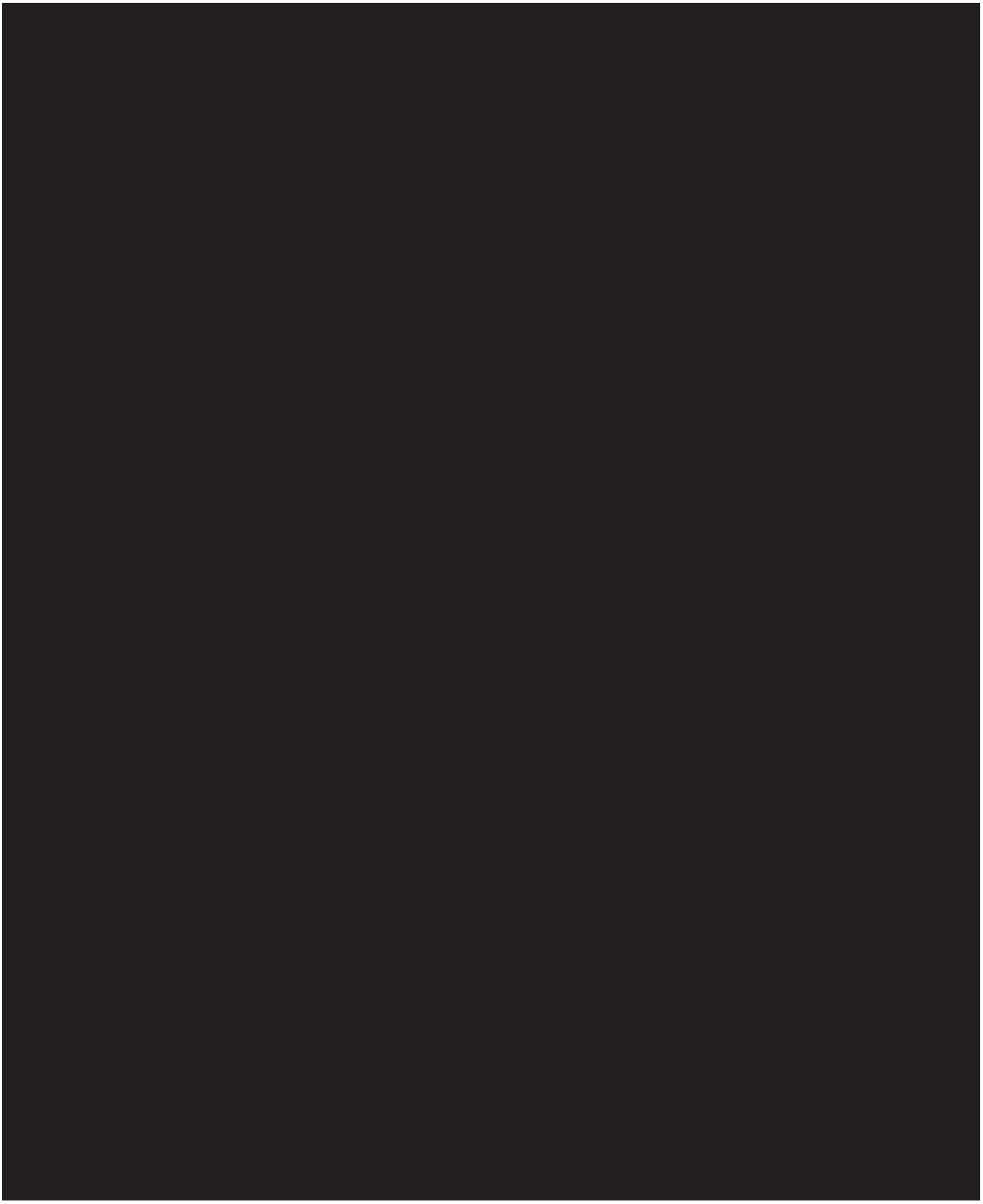
Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 3	*All*	*Date: 12-Sep-2019, version 1 (electronic 5.0)*
Amended Clinical Trial Protocol 2	*All*	*Date: 13-Dec-2018, version 1 (electronic 4.0)*
Amended Clinical Trial Protocol 1	*All*	*Date: 06-Apr-2018, version 1 (electronic 2.0)*
Protocol Amendment 6	*All*	*Date: 27-Jun-2018, version 2 (electronic 2.0)*
Amended Clinical Trial Protocol 2 (RU)	*Russia only*	*Date: 21-Apr-2017, version 1 (electronic 2.0)*
Protocol Amendment 5 (RU)	*Russia only*	*Date: 21-Apr-2017, version 1 (electronic 1.0)*
Amended Clinical Trial Protocol 2 (DE)	*Germany only*	*Date: 03-Jan-2017, version 1 (electronic 3.0)*
Protocol Amendment 4 (DE)	*Germany only*	*Date: 03-Jan-2017, version 1 (electronic 2.0)*
Amended Clinical Trial Protocol 1 (DE)	*Germany only*	*Date: 20-Jul-2016, version 1 (electronic 1.0)*
Protocol Amendment 3 (DE)	*Germany only*	*Date: 20-Jul-2016, version 1 (electronic 1.0)*
Amended Clinical Trial Protocol 1 (FR)	*France only*	*Date: 15-Jul-2016, version 1 (electronic 1.0)*
Protocol Amendment 2 (FR)	*France only*	*Date: 15-Jul-2016, version 1 (electronic 1.0)*
Amended Clinical Trial Protocol 1 (RU)	*Russia only*	*Date: 08-Mar-2016, version 1 (electronic 1.0)*
Protocol Amendment 1 (RU)	*Russia only*	*Date: 08-Mar-2016, version 1 (electronic 1.0)*
Clinical Trial Protocol		*Date: 14-Jan-2016, version 1 (electronic 1.0)*

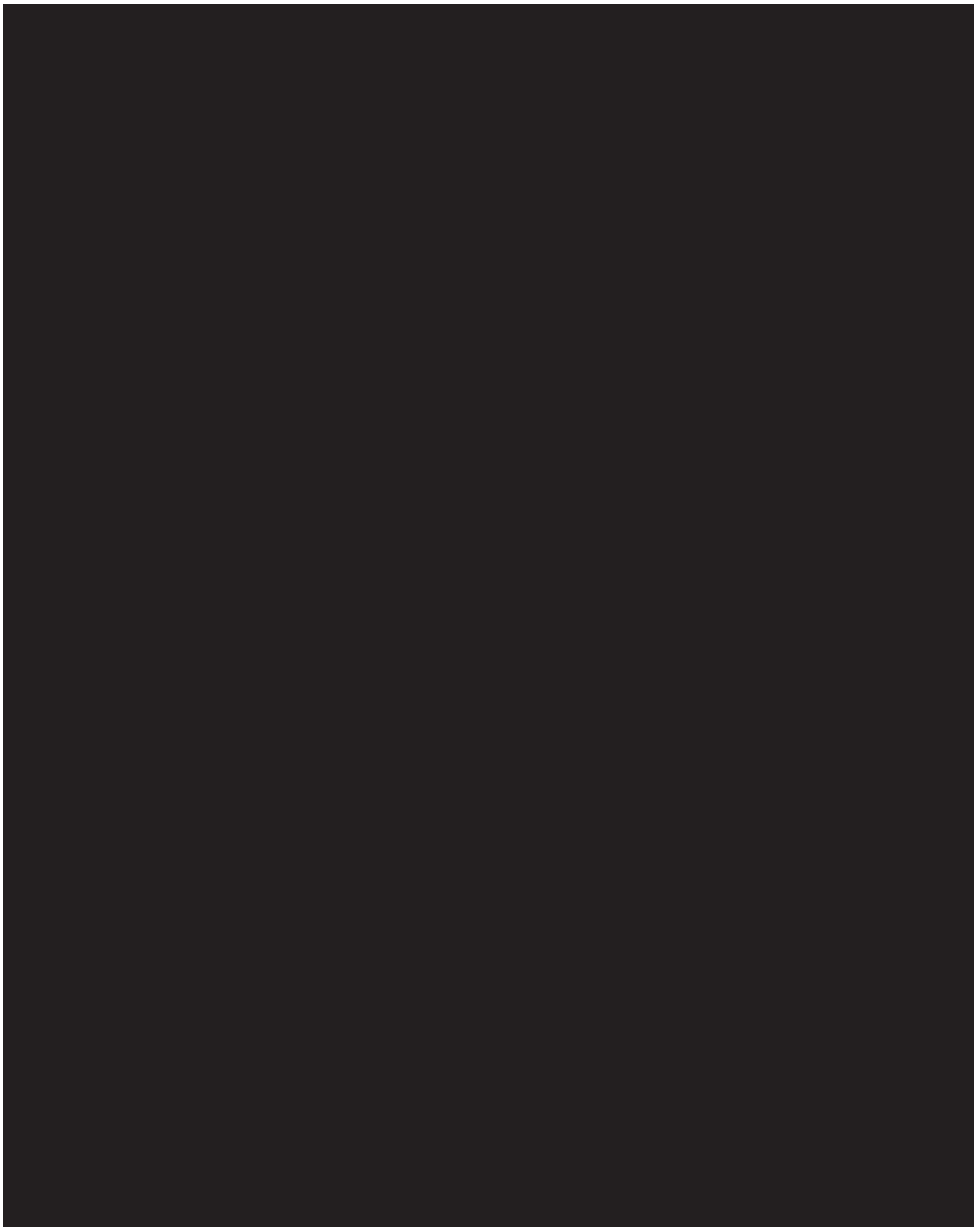
Amended protocol 03 (12-Sep-2019)

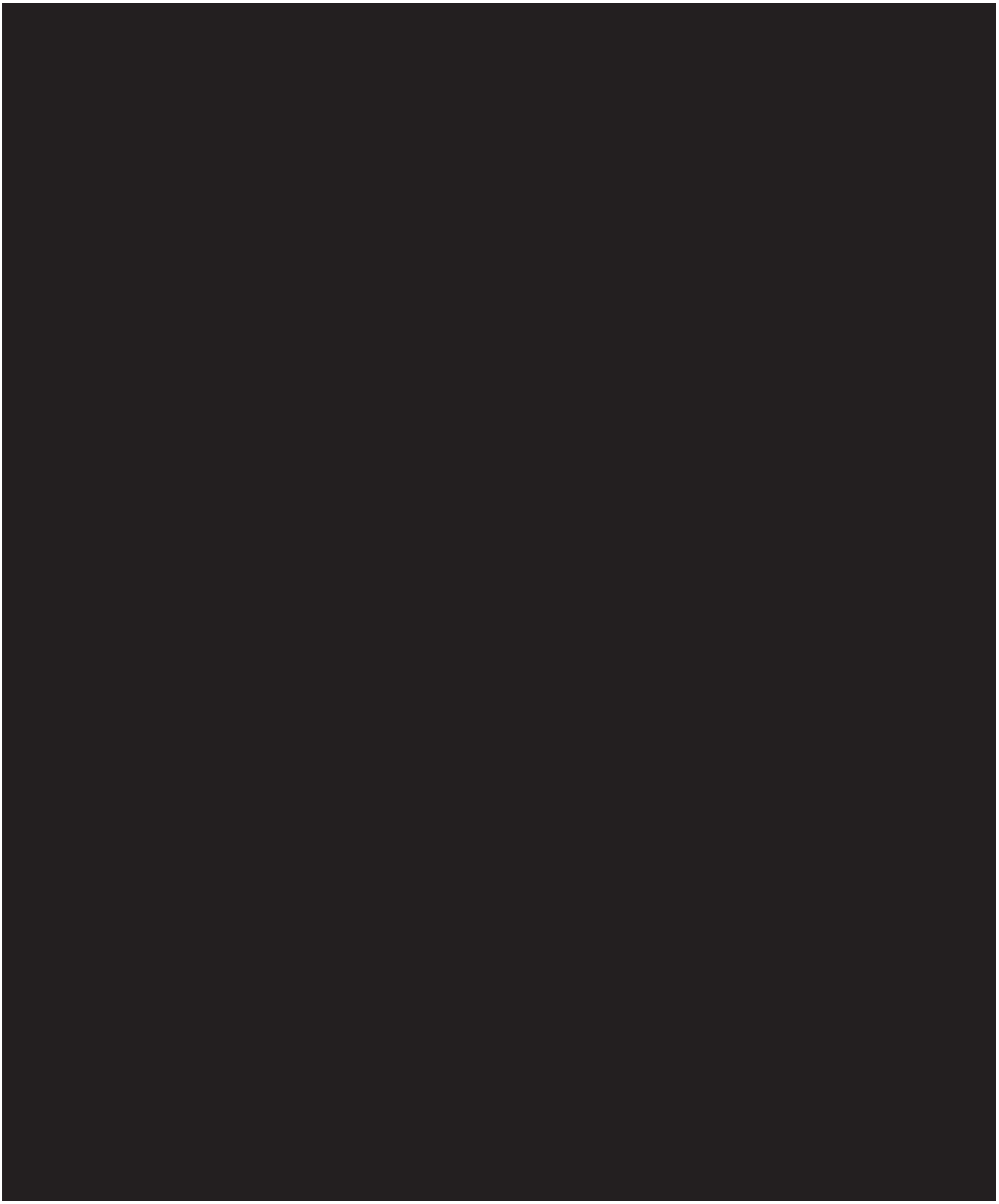
This amended protocol (amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

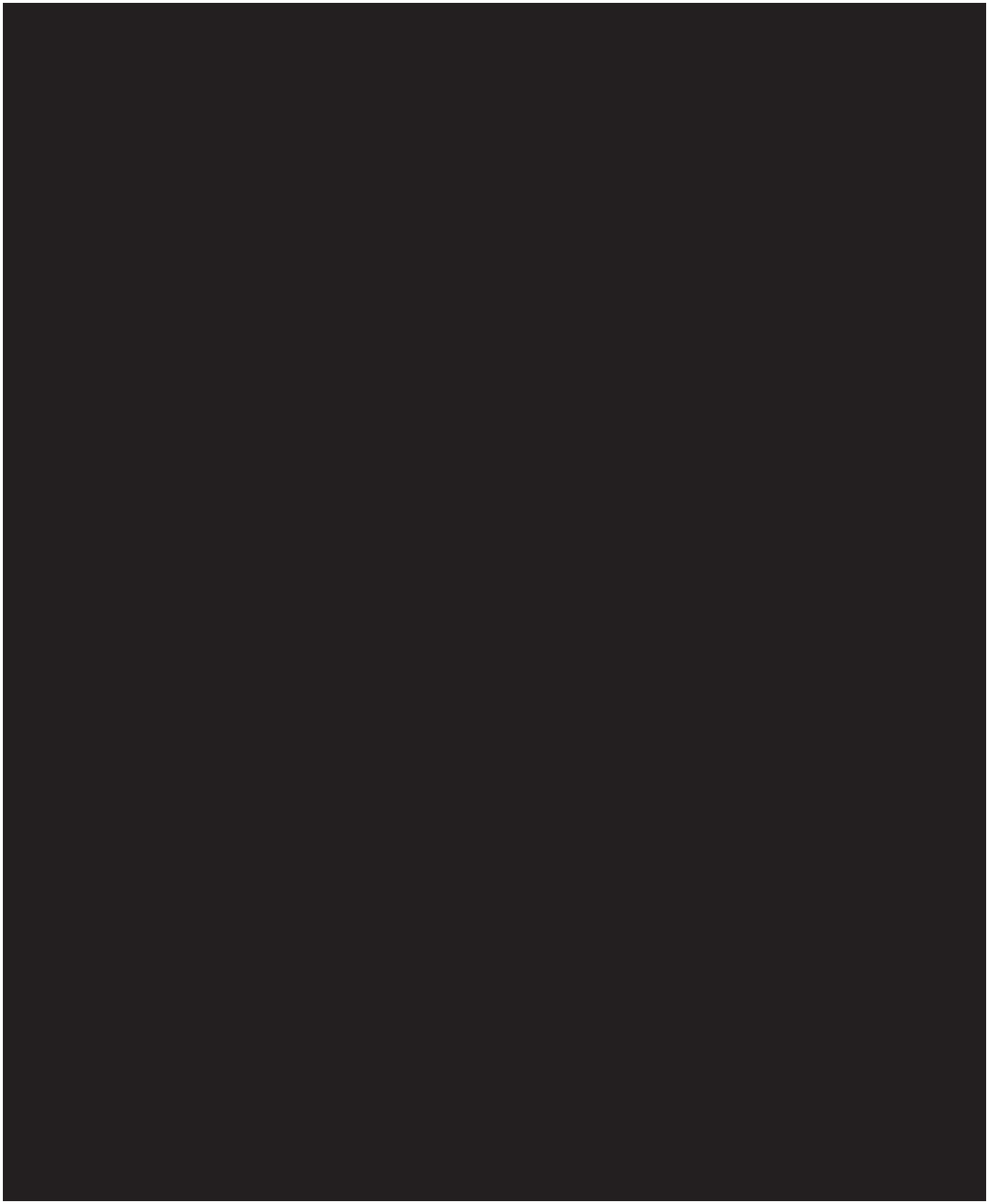
OVERALL RATIONALE FOR THE AMENDMENT

[redacted]









NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: Sarilumab/SAR153191	**STUDY No: DRI13925**
TITLE	An Open-label, Sequential, Ascending, Repeated Dose-finding Study of Sarilumab, Administered with Subcutaneous (SC) Injection, in Children and Adolescents Aged 2 to 17 Years, with Polyarticular-course Juvenile Idiopathic Arthritis (pcJIA) Followed by an Extension Phase
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	Phase 2b
STUDY OBJECTIVE(S)	**Primary objective:** To describe the pharmacokinetic (PK) profile of sarilumab in patients aged 2 to 17 years with pcJIA in order to identify the dose and regimen for adequate treatment of this population. **Secondary objectives:** To describe: • The pharmacodynamic (PD) profile and the efficacy of sarilumab in patients with pcJIA. • The long-term safety of sarilumab in patients with pcJIA.
STUDY DESIGN	**Design:** Multicenter, open–label, two-phase study in pcJIA patients from 2 to 17 years (or country specified age requirement) of age: The two phases are: **1) A 12-week core treatment phase, split into 3 portions:** • A first sequential, ascending dose-cohort, dose-finding portion (hereafter referred to as "dose-finding portion") in which up to 3 dose regimens will be investigated in two weight groups (Group A, patients ≥30 kg and ≤60 kg and Group B, patients <30 kg and ≥10 kg) in 6 evaluable patients per dose regimen weight group (around 36 patients in total). Patient enrollment will be staggered by weight group and dose regimen, starting with Group A and Dose Regimen 1 Cohort. • A subsequent portion (hereafter referred to as "second portion") where approximately 24 additional patients (12 in each weight group: patients ≥30 kg [Group A] and patients <30 kg and ≥10 kg [Group B]) will be enrolled directly to the selected dose regimen (identified based on the aggregate data from patients enrolled in the dose-finding portion) to achieve a total of 18 evaluable patients per weight group at this selected dose regimen. These patients will undergo the same 12-week core treatment phase assessments as patients recruited during the dose-finding portion. • A third portion (hereafter referred to as "third portion") where approximately 28 additional patients (a cap of 70% of each weight group: patients ≥30 kg [Group A] and patients <30 kg and ≥10 kg [Group B]) will be enrolled directly to the selected dose regimen to achieve a total of approximately 100 treated patients for the entire study. These patients will undergo the same on-site visits during the12-week core treatment phase as patients recruited in the dose-finding and second portions; however, the patients in the third portion will not have the sarilumab PK sampling visits between Baseline and Week 2. The 12-week core treatment phase is from Visit 2 (baseline-Week 0) to the time that Visit 12 investigational medicinal product (IMP) is administered.

For the dose-finding and second portions, during the 12-week core treatment phase, patients in the lower weight group, (Group B: <30 kg and ≥10 kg) will be randomly assigned to the following sarilumab PK sampling Schedule 1 or 2, in order to minimize the amount of blood withdrawn and the number of visits while maintaining the evaluation of the primary endpoint:

- Schedule 1: Baseline, Day 3, Day 8, Week 2, Week 4, Week 8, and Week 12
- Schedule 2: Baseline, Day 5, Day 12, Week 2, Week 4, Week 8 and Week 12.

2) An extension phase:

- A 144-week extension for patients enrolled in the dose-finding and second portions: The IMP at Visit 12 is considered as the first IMP for the extension phase. Only patients who have reached a Juvenile Idiopathic Arthritis (JIA) American College of Rheumatology (ACR) 30 response at Visit 12 (Week 12) will be permitted to continue in the extension phase. Patients will continue on the same dose regimen of sarilumab they were assigned to receive in the 12-week core phase of the study until the selected dose regimen is determined. Once the dose regimen is selected, patients who were not already on this dose regimen will have their dose regimen adjusted to the selected dose regimen, and will follow a new visit schedule with more frequent monitoring (for PK, safety, and efficacy) for the first 12 weeks compared to those patients who do not have their dose regimen adjusted.
- An 84-week extension for patients enrolled in the third portion. The IMP at Visit 12 is considered as the first IMP for the extension phase.

3) End-of-Treatment (EOT) and End-of-Study (EOS):

- For patients enrolled in the dose-finding and second portions: Patients who discontinue the study treatment prematurely will be assessed using the procedure for the End-of-Treatment (EOT) at Visit 27. These patients will be asked to return for the End-of-Study (EOS) assessment 6 weeks after the EOT visit (EOT + 6 weeks). For patients who prematurely discontinue the study treatment during the 12-week core treatment phase, there will be an additional sarilumab PK assessment 2 weeks after the EOT visit (EOT+ 2 weeks) and interleukin-6 (IL-6) and soluble interleukin-6 receptor (sIL-6R) will be measured at EOT visit. These patients will be asked to perform all the protocol scheduled visits and assessments except sarilumab administration until Visit 12.
- For patients enrolled in the third portion: Patients who discontinue the study treatment prematurely will be assessed using the procedure for the EOT at Visit 27 and will be asked to return for the EOS assessment 6 weeks after the EOT visit (EOT + 6 weeks). For patients who prematurely discontinue the study treatment during the 12-week core treatment phase, the IL-6 and sIL-6R will be measured at the EOT visit, and they will be asked to participate in all the protocol scheduled visits and assessments except sarilumab administration until Visit 12.

Tested dose regimens:

For each weight group, the 3 sequential ascending dose regimens to be tested were defined based on PK modeling with the following rationale:

- Dose Regimen 1: dose targeting PK exposures similar to sarilumab 150 mg once every other week (q2w), the lowest effective dose in adult patients with Rheumatoid Arthritis (RA)
- Dose Regimen 2: dose with targeted PK exposures similar to sarilumab 200 mg q2w in adult patients with RA
- Dose Regimen 3: dose targeting PK exposures similar to sarilumab 150 mg once per week (qw), which yielded the highest exposures in chronic dosing studies in adult patients with RA.

Body weight	Dose Regimen 1	Dose Regimen 2	Dose Regimen 3
Group A ≥30 kg and ≤60 kg	2 mg/kg q2w (6 patients)	3 mg/kg q2w (6 patients)	2 mg/kg qw (6 patients)
Group B <30 kg and ≥10 kg	2.5 mg/kg q2w (6 patients)	4 mg/kg q2w (6 patients)	2.5 mg/kg qw (6 patients)

Abbreviations: qw = once every week, q2w = once every other week.

The dose (mg) to be administered to patients will be calculated at baseline. The dose and corresponding volume of drug product will remain the same throughout the course of the 12-week core treatment phase of the trial regardless of change in patient's body weight. In the extension phase, the patient's weight will be measured at each visit and the dose will be adapted to the increase of weight only if the calculation shows a need for dose increase. The dose will be capped at 150 mg for Dose Regimens 1 and 3, and 200 mg for Dose Regimen 2, respectively.

Rules for stepwise approach

For permitting enrollment into Dose Regimen 1 Cohort for group B (<30 kg and ≥10 kg)

Enrollment in Dose Regimen 1 Cohort for Group B (<30 kg and ≥10 kg), will be initiated after the review of available safety, efficacy, PK, and PD data for a minimum of 3 out of the 6 patients planned in that same tested dose regimen cohort in Group A (≥30 kg and ≤60 kg) who have completed at least 4 weeks of study treatment.

For escalating the dose in a group

The decision to initiate the next dose regimen cohort in the same weight group will be taken by the Dose Escalation Committee (DEC) after review of at least 6 weeks of efficacy and safety data as well as the available PK and PD data for a minimum of 3 patients out of the 6 from the current dose regimen cohort in the weight Group A.

Dose Regimen 3 Cohort in weight Group B will be initiated based on DEC decision after review of efficacy and safety as well as all available PK and PD data from Dose Regimen 1 and 2 Cohorts of Groups A and B.

For prematurely stopping enrollment in a dose regimen cohort weight group

A dose regimen cohort for a weight group may be prematurely terminated after review of the 6-week data for at least 3 patients out of the 6 planned to be enrolled in that dose regimen cohort weight group if none of these patients have reached JIA ACR 30 response. All available efficacy, safety, PK, and PD data will be taken into account in making this decision.

If a dose is declared to be ineffective, no additional patients will be enrolled in that dose regimen cohort weight group and, if there is no major safety concern, the next dose regimen cohort will be initiated immediately. Any patient that has been included in that dose regimen cohort group will have to discontinue from the study treatment and receive the standard of care treatment as per the Investigator's clinical judgment.

	Rules for dose regimen selection The selection of the dose regimen will be made by the DEC after review of sufficient Week 12 PK, PD, efficacy, and safety data from patients enrolled in the dose-finding portion of the study.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** • Male and female patients aged ≥2 and ≤17 years (or country specified age requirement) at the time of the Screening visit • Diagnosis of rheumatoid factor (RF)-negative or RF-positive polyarticular JIA subtype or oligoarticular extended JIA subtype according to the International League of Associations for Rheumatology (ILAR) 2001 JIA Classification Criteria with at least 5 active joints as per ACR definition for "active arthritis" at Screening • Patient with an inadequate response to current treatment and considered as a candidate for a biologic disease modifying antirheumatic drug (DMARD) as per Investigator's judgment • The patient (who has reached the legal age of consent based on local regulations) or the parent(s) or the legal guardian(s) sign and date the Ethics Committee (EC) approved written informed consent. The patient's assent should be obtained based on local guidelines, the patient's maturity and intellectual capacities of understanding the study associated information. **Exclusion criteria:** • Body weight <10 kg or >60 kg for patients enrolled in the 3 ascending dose regimen cohorts, then body weight <10 kg for patients subsequently enrolled at the selected dose regimen cohorts • Wheelchair-bound or bed-ridden • Diagnosis of JIA subtypes except polyarticular RF-positive (RF+) or RF-negative (RF-) JIA or extended oligoarticular juvenile idiopathic arthritis (oJIA) • If nonsteroidal anti-inflammatory drugs (NSAIDs) (including cyclo-oxygenase-2 inhibitors [COX-2]) taken, dose stable for <2 weeks prior to the Baseline visit and/or dosing prescribed outside of approved label • If non-biologic DMARD taken, dose stable for <6 weeks prior to the Baseline visit or at a dose exceeding the recommended dose as per local labeling • If oral glucocorticoid taken, dose stable for <2 weeks or dose exceeding equivalent prednisone dose 0.5 mg/kg/day (or 30 mg/day) within 2 weeks prior to Baseline • Use of parenteral or intra-articular glucocorticoid injection within 4 weeks prior to Baseline • Prior treatment with anti- IL-6 or IL-6 receptor (IL-6R) antagonist therapies, including but not limited to tocilizumab or sarilumab • Treatment with any biologic treatment for pcJIA within 5 half-lives prior to the first dose of sarilumab as follows (the required off-treatment periods and procedures may vary according to local requirements): - Etanercept: within 4 weeks - Infliximab: within 8 weeks - Adalimumab: within 15 weeks - Anakinra: within 2 days - Canakinumab: within 19 weeks - Abatacept: within 10 weeks - Rituximab or other cell-depleting agent: within 16 weeks or until total lymphocyte count and CD 19+ lymphocyte count are normalized, whichever is longer

	- Intravenous (IV) immunoglobulin (Ig): within 15 weeks. • Treatment with a Janus kinase inhibitor within 4 weeks prior to the first dose of sarilumab; and treatment with growth hormone within 4 weeks prior to the first dose of sarilumab (the required off-treatment periods and procedures may vary according to local requirements) • Treatment with any investigational biologic or non-biologic product within 8 weeks or 5 half-lives prior to Baseline, whichever is longer • Lipid lowering drug stable for less than 6 weeks prior to Screening • Exclusion related to tuberculosis (TB): - Active TB or a history of incompletely treated TB - Purified Protein Derivative (PPD) or QuantiFERON-TB positive patients (no active disease) are excluded from the study, unless the following conditions are met: - It is documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist - No evidence of active TB infection indicated by the chest radiograph performed according to local guidance for the screening of TB infection prior to the study - Suspected extrapulmonary TB infection - Patients at high risk of contracting TB, such as close contact with individual with active or latent TB. • Exclusion criteria related to past or current infection other than tuberculosis: - History of invasive opportunistic infections, including but not limited to histoplasmosis, listeriosis, coccidioidomycosis, candidiasis, pneumocystis jirovecii, aspergillosis despite resolution, or John Cunningham (JC) virus (progressive multifocal leukoencephalopathy) - History of recurrent or active herpes zoster or reactivation or new onset of Epstein-Barr virus (EBV) or positive test for EBV within 2 months of the Screening (or at the Screening visit) - Diagnosed non tuberculous mycobacterial infection based on clinical, radiological and microbiological evidence within 2 months of the Screening (or at the Screening visit) - History of prior articular or prosthetic joint infection - Fever (>38°C), or chronic, persistent, or recurring infection(s) requiring active treatment with antibiotics, antivirals, or antifungals within 4 weeks prior to the Screening visit or other frequent recurrent infections deemed unacceptable, as per the Investigator judgment - Previous or at the Screening: hepatitis B surface antigen (HBs-Ag) positive, or total hepatitis B core antibody (HBc-Ab) positive; previous or at the Screening: Hepatitis C antibody positive - Patients who had a positive test previously or at the Screening for human immunodeficiency virus (HIV) test or who are suspected to be positive for HIV. • Any live, attenuated vaccine within 4 weeks prior to the Baseline visit, such as varicella-zoster, oral polio, rubella vaccines. Killed or inactive vaccine may be permitted based on the Investigator's judgment • Prior or current history of malignancy, including lymphoproliferative diseases, other than adequately-treated carcinoma in-situ of the cervix, nonmetastatic squamous cell, or basal cell carcinoma of the skin, within 5 years prior to the Baseline visit • Prior or current history of other significant concomitant illness (es) that, according to the Investigator's judgment, would adversely affect the patient's participation in the study. These include, but are not limited to, cardiovascular,

	renal, neurological disorders (including demyelinating disease), active infectious diseases, endocrinological, gastrointestinal, hepatobiliary, metabolic, pulmonary (eg, severe asthma, cystic fibrosis), nonmalignant lymphoproliferative diseases, other lymphatic disease(s), autoimmune disease, psychiatric disorders, etc • Patients with nonhealed/healing skin ulcers • Surgery within 4 weeks prior to the Screening visit or with planned surgery during the course of the study • History of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug and known hypersensitivity to any constituent of the product • History of inflammatory bowel disease, severe diverticulitis, or previous gastrointestinal perforation whatever the cause • Uncontrolled diabetes mellitus, defined as glycosylated hemoglobin (HbA1c) ≥9% at the Screening visit • Conditions/situations such as: - Patients with short life expectancy - Conditions/concomitant diseases making patients non-evaluable for the efficacy endpoints, eg, patients with chronic pain caused by conditions other than JIA, eg, fibromyalgia - Patients whose immediate family members are dependent (employee) of site/Investigator, and individuals who are institutionalized due to regulatory or legal order. • Any of the following laboratory abnormalities at the Screening visit (identified by the central laboratory): [redacted] • Pregnant or breast-feeding female adolescent patients (refer to main body of protocol for details).
Total expected number of patients	Assuming that 3 dose regimens will be tested and one of these 3 dose regimens will be selected, up to approximately 72 patients will be enrolled (to achieve approximately 60 evaluable patients) in the dose-finding and second portions. Approximately 28 additional patients will be enrolled in the third portion to achieve a total of approximately 100 treated patients for the entire study.
Expected number of sites	Approximately 45 sites (additional sites could be opened).
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation:**	Sarilumab, anti-interleukin 6 receptor alpha subunit (anti-IL-6R) monoclonal antibody. Vial: 175 mg/mL (2.7 mL filled with 2.0 mL extractible volume).

Route(s) of administration:	Route of administration: subcutaneous (SC). Injection sites: abdomen (alternated between the 4 quadrants), thighs, and upper arms lateral side (upper arm lateral side not appropriate for self-injection).
Dose regimen:	Dose Regimen 1: • Group A (≥30 kg and ≤60 kg): 2 mg/kg q2w • Group B (<30 kg and ≥10 kg): 2.5 mg/kg q2w. Dose Regimen 2: • Group A (≥30 kg and ≤60 kg): 3 mg/kg q2w • Group B (<30 kg and ≥10 kg): 4 mg/kg q2w. Dose Regimen 3: • Group A (≥30 kg and ≤60 kg): 2 mg/kg qw • Group B (<30 kg and ≥10 kg): 2.5 mg/kg qw. Volumes for Dose Regimens 1 to 3 to be injected depending on patient's weight at Baseline are further detailed in the protocol Appendix B. The dose regimen of the selected dose will be one of these 3 dose regimens, or an intermediate dose regimen based on DEC review of the sufficient Week 12 PK, PD, efficacy, and safety data from the patients enrolled in the dose-finding portion of the study. The dose will be capped at 150 mg for Dose Regimens 1 and 3, and 200 mg for Dose Regimen 2, respectively.
Noninvestigational medicinal product(s) (if applicable):	N/A
Route(s) of administration:	N/A
Dose regimen:	N/A
ENDPOINT(S)	**Primary endpoint:** • Sarilumab PK exposure (maximum serum concentration observed [C_{max}] and area under the serum concentration versus time curve using the trapezoidal method during a dose interval [$AUC_{0-\tau}$]), following the first dose, concentration observed before treatment administration during repeated dosing (C_{trough}) from baseline to Week 12. **Secondary endpoint(s):** **12-week core treatment phase** • Safety - Adverse events (AEs), vital signs, physical examination, laboratory values - Acceptability assessments (local tolerability). • Efficacy - Juvenile Idiopathic Arthritis ACR 30/50/70/90/100 response rate at Week 12 - Change from baseline in individual JIA ACR components at Week 12 - Juvenile Arthritis Disease Activity Score - 27 change from baseline at Week 12. • Pharmacodynamics - Changes in IL-6 associated biomarkers [eg, serum levels of high sensitivity C-reactive protein (hs-CRP), IL-6, total sIL-6R].

	Extension phase • Safety - Adverse events, vital signs, physical examination, laboratory values - Acceptability assessments (local tolerability). • Efficacy - JIA ACR 30/50/70/90/100 response rate at Weeks 24 and 48, and every 24 weeks up to the end of the study (EOS) - Change from baseline in individual JIA ACR components at Weeks 24 and 48, and every 24 weeks up to EOS - Juvenile Arthritis Disease Activity Score – 27change from baseline at Weeks 24 and 48, and every 24 weeks up to EOS.
STATISTICAL CONSIDERATIONS	[redacted] **Analysis populations:** The **efficacy** population will consist of all included patients who receive at least 1 dose of sarilumab. All patients should be followed at least to the end of the 12-week core treatment phase and will be analyzed according to the treatment that they actually receive. The **PK** population will consist of all included patients who receive at least 1 dose of sarilumab and have at least one post-dose drug concentration. All patients will be analyzed according to the treatment that they actually receive.

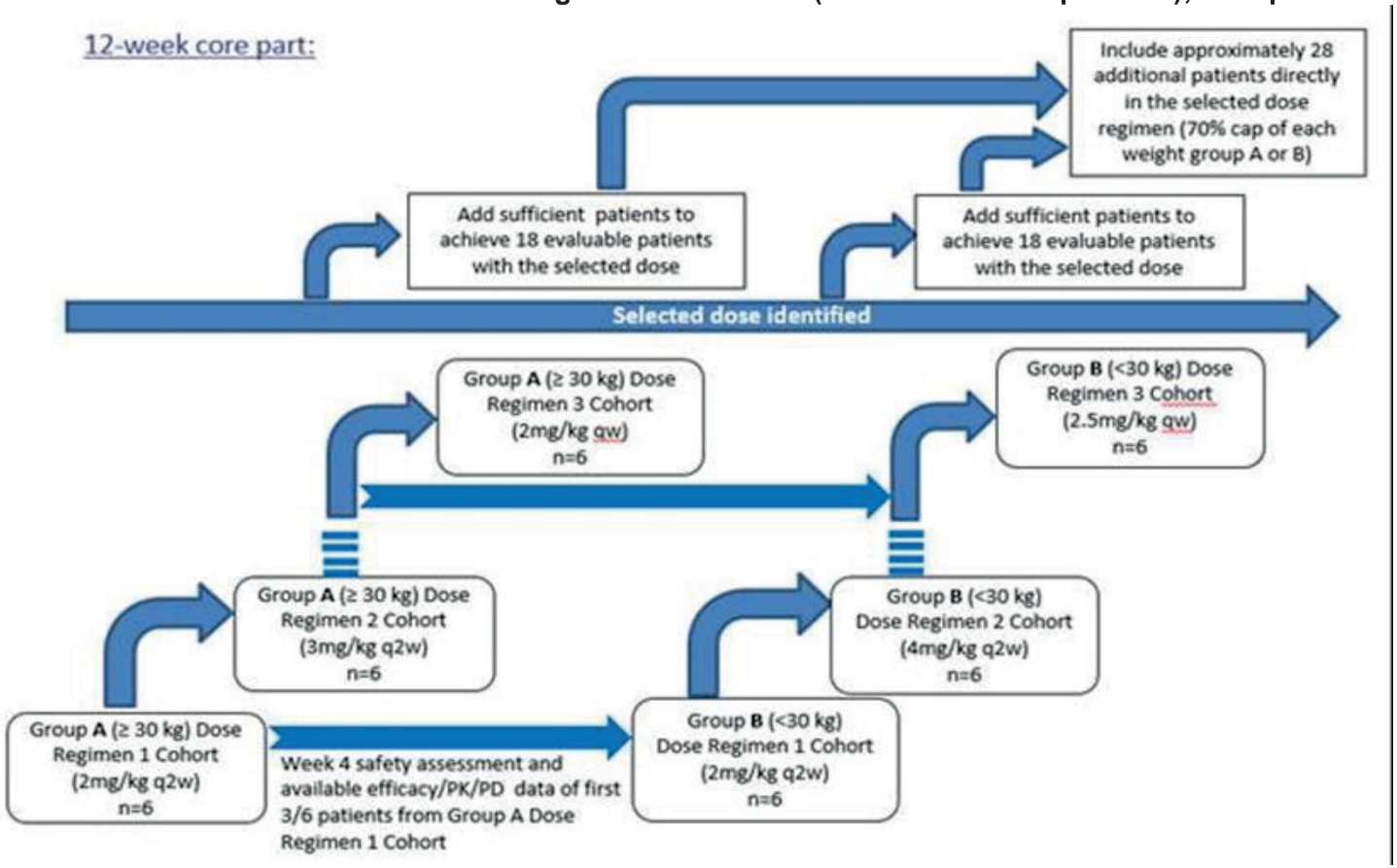
	The **safety** population will consist of all included patients who receive at least 1 dose or part of a dose of sarilumab. All patients will be analyzed according to the treatment that they actually receive. **Primary Analysis:** [redacted] will be used to estimate sarilumab PK parameters and the effects of age, weight, and other intrinsic factors on these PK parameters. **Analysis of efficacy endpoints** Juvenile Idiopathic Arthritis ACR 30 response rates for each dose and weight group will be summarized by visit, and the mean (SD) of the JIA ACR component scores, PD parameters, and their changes from baseline calculated. Juvenile Idiopathic Arthritis ACR 50/70/90/100 will be summarized using the same primary approach as for ACR30. Overall score and change from baseline in JADAS-27 will be summarized by visit (including number, mean, and standard error, SD, median, minimum, and maximum) for each dose regimen cohort and weight group (if possible). [redacted] [redacted] **Safety** Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), TEAEs leading to treatment discontinuation and treatment-emergent adverse events of special interest (AESIs) will be summarized for each treatment group based on Medical Dictionary for Regulatory Activities (MedDRA) coding of verbatim terms reported by Investigators. For laboratory parameters and vital signs, incidences of potentially clinically significant abnormality (PCSA) values, actual values and change from baseline will be summarized by treatment group. The number of patients with neutropenia will be summarized by maximum grade during the TEAE period for each treatment group. The group means of absolute neutrophils counts (ANC) with standard deviations will be displayed graphically over time. Similar analyses will be performed for ALT elevations and changes in serum lipids. **Planned database lock date:** The first database lock will occur once sufficient Week 12 data have been observed from the dose-finding portion of the study to allow a selection of a dose regimen for more detailed investigation. If the enrollments for weight Group B are not completed within a similar time frame as that for weight Group A, the dose selection on weight Group A will be done separately from the dose selection on weight Group B, ie, 2 separate data analyses will be needed. The second database lock will occur approximately 1 year from the time every patient enrolled in the dose-finding and second portions has received the selected dose regimen (either new enrolled patients or patients already in the extension phase). The third database lock will occur approximately 1 year from the time the last patient is enrolled in the third portion. The final database lock will occur approximately 4 weeks after the last patient has completed the EOS visit.

DURATION OF STUDY PERIOD (per patient)	- Total study duration of up to 166 weeks for patients enrolled in the dose-finding and second portions and up to 106 weeks for patients enrolled in the third portion (per patient): • Up to 4 weeks +3 days Screening (maximum 31 days) • 12 weeks core treatment phase • Up to 144 weeks extension phase for patients enrolled in the dose-finding and second portions and up to 84 weeks extension phase for patients enrolled in the third portion • 6 weeks post-treatment follow-up. For all visits, a time frame of ±1 day for Dose Regimen 3 Cohort and ±3 days for Dose Regimen 1 and 2 Cohorts is acceptable using Day 1 as reference except for: • For Visit 3 (Day 3), Visit 4 (Day 5) and Visit 5 (Day 8), no sample collection window is allowed where PK sampling occurs • Visit 6 (Day 12) ±1 day for all applicable dose regimen cohorts • Visit 7 (Week 2) ±1 day for all dose regimen cohorts • Visit 8 (Week 4) ±2 days for Dose Regimen 1 and 2 Cohorts and ±1 day for Dose Regimen 3 Cohort.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN

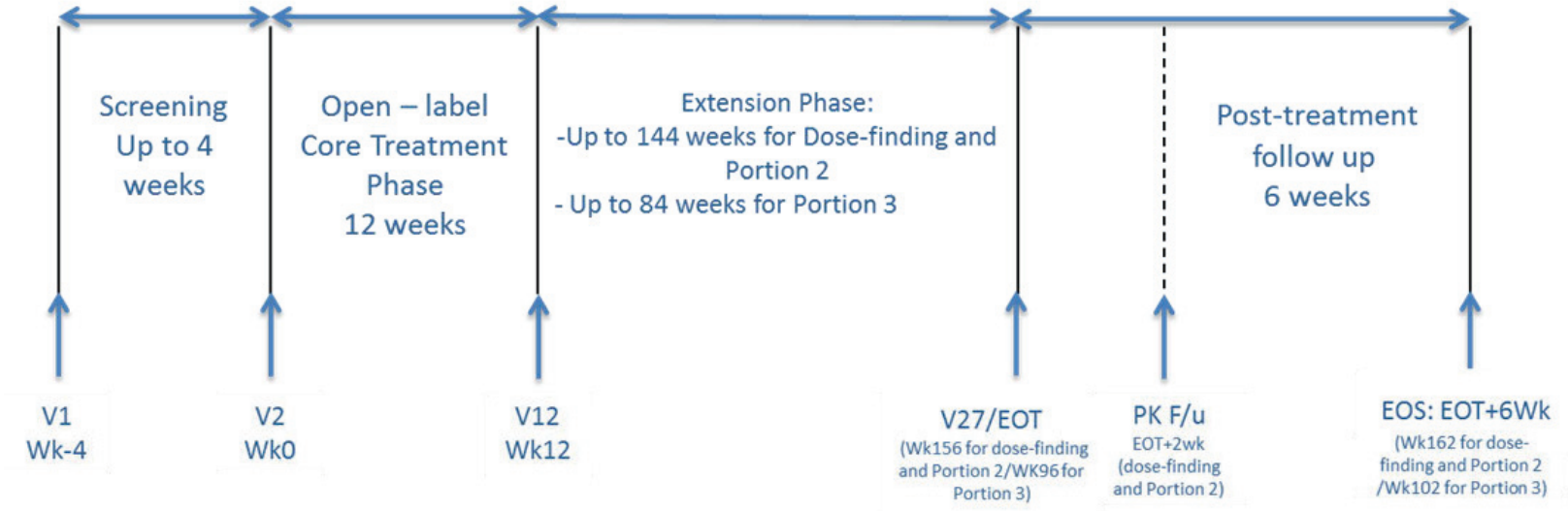
1.1.1 Graphical study design for dose regimen cohorts: Group A: ≥30 kg and ≤60 kg for the dose-finding (first) portion and ≥30 kg for patients enrolled once the selected dose regimen is identified (second and third portions); Group B: ≥10 kg and <30 kg



PD= pharmacodynamics, PK= pharmacokinetic, qw= once a week, q2w= once every other week.

Notes: Enrollment in Group B (<30 kg and ≥10 kg) will initiate after the review of safety and available data from the first 3 out of the 6 patients planned in the first tested dose regimen in Group A (≥30 kg and ≤60 kg) who have completed at least 4 weeks of study treatment.

1.1.2 Study flow diagram



Abbreviations: EOS = end-of-study, EOT = end-of-treatment, PK = pharmacokinetic, V = visit, Wk = week
Notes: All patients must complete an end-of-treatment (EOT) visit (V27, Week 156 for dose-finding and second portions/Week 96 for third portion) at the completion of treatment (last IMP injection at Week 154/Week 94 for Dose Regimens 1 and 2 Cohorts and at Week 155 for Dose Regimen 3 Cohort) or at the time of early permanent treatment discontinuation (regardless of treatment phase).
For a patient who discontinues study treatment prematurely during the 12-week core treatment phase, interleukin-6 (IL-6) and soluble interleukin-6 receptor (sIL-6R) will be measured at EOT visit. For patients in the dose-finding and second portions who discontinue study treatment prematurely during 12-week core treatment phase, an additional PK visit, 2 weeks after the EOT visit is required for blood sampling (V88).
All patients must complete a post-treatment follow-up visit (V28) 6 weeks after the EOT visit. However, patients discontinuing treatment prematurely during the core treatment phase should continue to return for the study visits as protocol scheduled without treatment administration through Week 12 (as per Food and Drug Administration (FDA) guidelines for missing data).

1.2 STUDY FLOW CHARTS

1.2.1 12-week core treatment phase

All patients will undergo the initial 12-week core treatment phase (ie, those recruited during the initial [dose-finding] portion and those subsequently enrolled directly to the selected dose regimen in the second and third portions).

	Screening (4 weeks)	Baseline visit	Core treatment phase (12 weeks)										PK Follow-up[a]
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V88 EOT + 2 Weeks (for patients who discontinue the study treatment during the core treatment phase or not going to enter the extension phase)
Day	D-28 to D-1 (+3) (Maximum 31 days)	D1	D3[b]	D5[b]	D8[b]	D12[b] (±1)	D15 (±1)	D29 (±1 or 2)	D43 (±1 or 3)	D57 (±1 or 3)	D71 (±1 or 3)	D85 (±1 or 3)	
Week		Wk 0					Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	
Eligibility[c]													
Written informed consent and patient assent form[d]	X												
Inclusion/exclusion criteria[c]	X	X											
Ethnicity and race	X												
Patient demography	X												
Tanner stage and menstruation status	X											X	
Medical/surgical history	X												
Prior medications/vaccination history	X												
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Home diary/compliance[e]		X					X	X	X	X	X	X	

	Screening (4 weeks)	Baseline visit	Core treatment phase (12 weeks)										PK Follow-up[a]
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V88 EOT + 2 Weeks (for patients who discontinue the study treatment during the core treatment phase or not going to enter the extension phase)**
Day	**D-28 to D-1 (+3) (Maximum 31 days)**	**D1**	**D3[b]**	**D5[b]**	**D8[b]**	**D12[b] (±1)**	**D15 (±1)**	**D29 (±1 or 2)**	**D43 (±1 or 3)**	**D57 (±1 or 3)**	**D71 (±1 or 3)**	**D85 (±1 or 3)**	
Week		**Wk 0**					**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	
Physical examination[f]	X	X						X	X			X	
Optional: EBV, Hepatitis B and C and HIV[g]	X												
PPD tuberculin skin test for patients ≤5 yrs; QuantiFERON-TB test for patients >5 yrs[h]	X												
Chest X-ray[i]	X												
Confirm eligibility		X											
Call IVRS	X	X					X	X	X	X	X	X	
IMP administration													
IMP administration[j]		X			X[j]		X	X	X	X	X	X	
IMP dispense[k]		X					X	X	X	X	X	X	
Vital signs and body measurement													
Temperature, heart rate, blood pressure	X	X						X		X		X	
Weight	X	X										X	
Height (stadiometer)[l]	X	X										X	

	Screening (4 weeks)	Baseline visit	Core treatment phase (12 weeks)										PK Follow-up[a]
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V88**
Day	**D-28 to D-1 (+3) (Maximum 31 days)**	**D1**	**D3[b]**	**D5[b]**	**D8[b]**	**D12[b] (±1)**	**D15 (±1)**	**D29 (±1 or 2)**	**D43 (±1 or 3)**	**D57 (±1 or 3)**	**D71 (±1 or 3)**	**D85 (±1 or 3)**	**EOT + 2 Weeks (for patients who discontinue the study treatment during the core treatment phase or not going to enter the extension phase)**
Week		**Wk 0**					**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Wk 12**	
Efficacy assessment													
JIA ACR disease core set[m]	X	X					X	X	X	X	X	X	
JADAS-27[n]		X										X	
Safety assessments													
Adverse event/SAE recording	|----------												----------|
Tuberculosis risk assessment	X	X					X	X	X	X	X	X	
Local tolerability		X			X		X	X	X	X	X	X	
Laboratory testing													
Hematology[o]	X	X[o]		X[o]		X[o]	X	X	X	X	X	X	
Chemistry[p]	X[p]	X[p]					X	X	X	X	X	X[p]	
Fasting lipids[q]	X							X				X	
Optional: glycosylated hemoglobin (HbA1c)[r]	X												
hs-CRP	X	X					X	X	X	X	X	X	
ESR		X										X	
Rheumatoid factor (RF)		X											
ANA/anti-dsDNA antibody		X										X	
Urinalysis[s]	X												

	Screening (4 weeks)	Baseline visit	Core treatment phase (12 weeks)										PK Follow-up[a]
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V88 EOT + 2 Weeks (for patients who discontinue the study treatment during the core treatment phase or not going to enter the extension phase)
Day	D-28 to D-1 (+3) (Maximum 31 days)	D1	D3[b]	D5[b]	D8[b]	D12[b] (±1)	D15 (±1)	D29 (±1 or 2)	D43 (±1 or 3)	D57 (±1 or 3)	D71 (±1 or 3)	D85 (±1 or 3)	
Week		Wk 0					Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	
Serum pregnancy for females who are menstruating[t]	X												
Local urine pregnancy test for females who are menstruating[u]		X						X		X		X	
Pharmacokinetics, ADA, and pharmacodynamics													
Serum sarilumab PK[v] Group A (≥30 kg and ≤60 kg)		X	X	X	X	X	X	X		X		X	X
Serum sarilumab PK[v] Group B (<30 kg and ≥10 kg) Schedule 1		X	X		X		X	X		X		X	X
Serum sarilumab PK[v] Group B (<30 kg and ≥10 kg) Schedule 2		X		X		X	X	X		X		X	X
Antibodies to sarilumab[v]		X										X	
IL-6 and total sIL-6R[w]		X										X	
Pharmacogenomics (optional)													
Saliva sample collection[x]		X											

Abbreviations: ADA = anti-drug antibody, ANA = antinuclear antibodies, BP = blood pressure, DNA = deoxyribonucleic acid, D = day, EBV = Epstein–Barr virus, EC = ethics committee, EOT = End-of-Treatment, ESR = erythrocyte sedimentation rate, HbA1c = glycosylated hemoglobin, HIV = human immunodeficiency virus, hs-CRP= high sensitivity C-reactive protein, Ig = immunoglobulin, IVRS = Interactive Voice Response System, IL = interleukin, IMP = investigational medicinal product, JADAS = Juvenile Arthritis Disease Activity Score, JIA ACR = Juvenile Idiopathic Arthritis American College of Rheumatology, PK = pharmacokinetics, PPD = Purified Protein Derivative, SAE = serious adverse event, sIL-6R = soluble Interleukin-6 receptor, TB = tuberculosis, V = visit, Wk = week, yrs = years.

a. For patients who discontinue treatment during the 12-week core treatment phase (at or before Visit 12), there will be an additional sarilumab PK assessment 2 weeks after the EOT visit (EOT+2 weeks). For patients enrolled in the third portion, Visit 88 is not applicable.
b. Sarilumab PK sampling between Visit 2 and Visit 7 vary between patients: Visit 3 (Day 3), Visit 4 (Day 5), Visit 5 (Day 8), Visit 6 (Day 12) for Group A (≥30 kg); on visits and days of Visit 3 (Day 3), Visit 5 (Day 8) for Group B (<30 kg) schedule 1; on visits and days of visits: Visit 4 (Day 5), Visit 6 (Day 12) for Group B (<30 kg) schedule 2 (see Section 9.1.1 and flow chart Section 1.2.1 for sample collection schedule and Section 6.3.1 for visiting/dosing windows). Sarilumab PK sampling could be performed at home. A PK diary will be provided to capture date and time of sample collection. No sample collection window is allowed for Visit 3 (Day 3), Visit 4 (Day 5) and Visit 5 (Day 8). There is ±1 day window allowed for Visit 6 (Day 12). Please refer to Section 10.1.3 and Section 9.3.4 for the additional hematology test during the sarilumab PK sampling period. For patients enrolled in the third portion, Visits 3, 4, 5, and 6 are not applicable. However, an additional hematology test must be performed before the second sarilumab administration (see footnote "o" for details).
c. At the Investigators' discretion laboratory tests mentioned in exclusion criterion E 24 may be repeated by central laboratory retesting between the Screening visit and the first IMP administration to ensure the patient meet eligibility with respect to exclusion criterion E 24. A locally approved specific consent form will be signed by patients who require Gilbert syndrome genetic testing (consent/assent must be obtained prior to performing this assessment and local regulations should be respected).
d. Prior to all screening assessments, the patient (if he/she has reached the legal age of consent based on the local regulations), the parent(s) or the legal guardian(s) must sign and date the EC approved written informed consent form. The patient, the parent(s) and the legal guardian(s) will receive information on the study objective(s) and procedures from the Investigator. Separate written consent forms should be obtained from the parent(s) or the legal guardian(s) who allows his/her child to participate in an optional saliva sample collection for pharmacogenomic study and give permission to the Sponsor to keep their left- over/unused blood samples for future research (see Section 10.1.1, Section 9.9, and Section 9.11). A separate (locally approved) informed consent form will be completed by any patients requiring genetic Gilbert disease testing as per local regulations. The signed assent forms should be obtained from the patient based on local regulations and his/her maturity of understanding the study information.
e. Home diary for IMP administration to be completed for IMP administered at home.
f. Complete physical examinations will be performed at Visit1 (Day -28 to Day -1, up to 31 days), Visit 2 (Day 1, Week 0), Visit 8 (Week 4), Visit 9 (Week 6), and Visit 12 (Week 12) including skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.
g. Optional: Based on the Investigator's judgment, Epstein-Barr virus (EBV) titer including IgG and IgM may be performed at the Screening; based on the patient's family and medical history and the Investigator's judgment, hepatitis B surface antigen (HBs-Ag), hepatitis B surface antibody (HBs-Ab), total hepatitis B core antibody (HBc-Ab), and hepatitis C antibody (HCV-Ab) may be performed at the Screening. The HIV serology will be performed only based on the Investigator's assessment for those HIV suspected patients. For Argentina and Germany only: Serology testing for hepatitis B and C and HIV have to be performed at Screening visit for all patients in order to screen corresponding exclusion criterion E 14.
h. Purified Protein Derivative (PPD) skin test should be performed in patients ≤5 years old prior to the Baseline Visit 2 (Day 1, Week 0). Patients should be evaluated within 48 to 72 hours after placement of the PPD skin test. For patients who fail to be evaluated within 72 hours, the skin test should be repeated. An assessment of the level of risk (TB contact and/or recent immigration from a country with a high prevalence of TB) vaccination history should be taken into consideration when defining the result of the skin tests. Refer to exclusion criteria E 13 for all the details. An interferon-gamma (IFN-r) release assay, QuantiFERON-TB test will be performed for patients >5 years old. (1) After the initial TB screening, if PPD or QuantiFERON result is negative, but clinical suspicion for TB is higher than moderate, the patient should be retested for TB at any time during the study based on the Investigator's assessment. QuantiFERON-TB test will be considered in the younger group of patients (≤5 years) based on the local PPD availability, local regulation for TB screening and the Investigator's judgment.
i. The chest X-ray may be performed for the patients only when deemed necessary based on the Investigator's judgment or in line with local guideline for TB screening prior to initiating a biologic therapy for JIA patients who haven't had a chest X-ray performed within 3 months prior to the Baseline Visit 2 (Day1, Week 0).
j. Investigational medicinal product to be administered once every other week for patients in Dose Regimen 1 and 2 Cohorts and once every week for patients in Dose Regimen 3 Cohort. Arrangements will be made for home nurses to administer IMP for Dose Regimen 3 Cohort patients for the intermediate visits (home administration if possible). Patients should be monitored for at least 30 minutes after IMP administration for any signs or symptoms of a hypersensitivity reaction. For Germany only: After the first IMP administration the patient has to be monitored for at least 1 hour to assess local tolerability. In the dose-finding and second portions, patients who do not achieve a JIA American College of Rheumatology (ACR) 30 by the end of the 12-week core treatment period will be discontinued from the study treatment to receive standard of care as per the Investigator's clinical judgment. Juvenile Idiopathic arthritis ACR response, including JIA ACR30 response, will be provided by the Sponsor to Investigator to evaluate this criterion only after Visit 12. For patients completing the core treatment phase at Visit 12 (Week 12), but not continuing to the extension phase for reasons other than lack of JIA ACR30 response, there will be no IMP injection at Visit 12.
k. Investigational medicinal product will be dispensed to patients who are at the Dose Regimen 3 Cohort during the core treatment phase.

l. Height will be measured using stadiometer at sites during the study.
m. Juvenile Idiopathic Arthritis ACR core set includes: global assessment of the severity of disease by the physician, global assessment of overall well-being by the patient or the parent(s)/guardian(s), number of joints with active arthritis (defined as swelling not due to deformity OR limitation of motion with either pain or tenderness or both), number of joints with limitation of motion, Childhood Health Assessment Questionnaire (CHAQ), hs-CRP (2,3,4). At the Screening, only number of joints with active arthritis and number of joints with limitation of motion will be assessed.
n. Juvenile Arthritis Disease Activity Score scoring is explained in Section 9.4.2.
o. Hematology (blood should be drawn PRIOR TO drug administration): Hemoglobin, hematocrit, red blood cell (RBC) count, and morphology (if RBC count is abnormal), white blood cell (WBC) differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count, absolute neutrophil count (ANC). An additional hematology test must be performed at Visit 6 (Day 12±1 day) for Dose Regimens 1 and 2 Cohorts in order to get the results before the second dose of sarilumab administration (Visit 7: Week 2, Day 15) or prior to or at Visit 5 (Day 8) for Dose Regimen 3 Cohort (not before Visit 4 [Day 5]) in order to get the results before second dose of sarilumab administration. For patients enrolled in the dose-finding and second portions, the additional hematology test can be done at the central laboratory or at the local laboratory to confirm the neutrophil count and platelet count before the second dose of sarilumab administration. For patients enrolled in the third portion without on-site Visit 6, the additional hematology test will be done at the local laboratory before the second dose of sarilumab administration, but no earlier than Day 12. If local laboratory is used, a central laboratory sample for hematology should still be drawn pre-IMP administration at Visit 7 (Day 15, Week 2) as scheduled for Dose Regimens 1 and 2 Cohorts and Visit 5 (Day 8) for Dose Regimen 3 Cohort. For all patients, the Visit 2 (Day 1) and additional hematology laboratory assessment must be reviewed before the administration of the second dose of sarilumab at Visit 5 (Day 8) for Dose Regimen 3 Cohort patients or at Visit 7 (Week 2, Day 15) for Dose Regimens 1 and 2 Cohort patients.
p. Chemistry (blood should be drawn BEFORE drug administration): Whole chemistry will be performed at the Screening visit, Baseline Visit 2 (Day1, Week 0) and Visit 12 (Week 12) or EOT only: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, and creatinine clearance, glomerular filtration rate (using the modified Schwartz formula), calcium, phosphate, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, conjugated bilirubin, and unconjugated bilirubin. At all other visits: only ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and albumin will be tested.
q. Fasting lipids (blood should be drawn BEFORE drug administration): Triglycerides (TG), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol. Patients are required to fast at least 8 hours before the test.
r. Optional: HbA1c levels will be only measured based on the patient's medical history and Investigator's judgment.
s. Urinalysis dipstick: specific gravity, pH, glucose, blood, protein, nitrates, leukocyte esterase, bilirubin. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
t. For females who have commenced menstruating, a serum pregnancy test is mandatory at the screening visit.
u. For females who have commenced menstruating, a urine pregnancy local test should be performed at Visit 2 (Week 0, Day 1), Visit 8 (Week 4), Visit 10 (Week 8), and Visit 12 (Week 12). The urine pregnancy test can be performed locally. The pregnancy status should be checked by urine pregnancy testing prior to exposure to the IMP and EOT.
v. Blood samples will be collected PRIOR TO IMP administration on the dosing days during the treatment period. If SAE occurs in a patient, blood samples should be collected for determination of sarilumab concentration and anti-drug antibody (ADA) assessment at or near the onset and completion of the occurrence of the event, if possible (see Section 9.1). In the dose-finding and second portions, if a patient discontinues study treatment prematurely during the 12-week core treatment phase, an additional PK Visit, 2 weeks after the EOT visit is required for blood sampling (Visit 88).
w. For patients who prematurely discontinue the study treatment during the core treatment phase, the IL-6 and total sIL-6R will be measured at the EOT assessment.
x. Parent(s) or legal guardian(s) must sign a separate informed consent form prior to optional saliva sample collection for phamacogenomic study. Samples are preferred to being collected at the Baseline Visit 2 (Day 1, Week 0), but can be collected at any visit. The patient can also sign the informed consent form based on his/her age, local regulations, and his/her maturity of understanding the study information. The patient is still eligible to enroll in the study if he/she or his/her parent(s) or his/her legal guardian(s) do not wish him/her to participate in saliva sample collection.

1.2.2 Extension phase

In the dose-finding and second portions, only patients achieving at least a JIA ACR30 response at Week 12 will be permitted to continue to participate in the extension phase.

During the extension phase:

- Patients who were enrolled to the selected dose regimen during the core treatment phase (either during the initial dose-finding portion or directly to the selected dose regimen in the second portion) will continue on the selected dose regimen during the extension phase and will be followed-up as noted in Section 1.2.2.1)
- Once the selected dose regimen has been determined, patients who were not assigned to the selected dose regimen will have their dose regimen adjusted to the selected dose regimen during the extension phase. Prior to dose adjustment, these patients will complete the assessments as noted in Section 1.2.2.1. After the dose regimen is determined, the patients will have their dose regimen adjusted to the selected dose regimen at the time of their next regular scheduled visit (according to Section 1.2.2.1), which will be considered as the first visit (Visit 101 [Week 0]) as shown in the flow chart in Section 1.2.2.2. These patients will then continue with the assessments as noted in Section 1.2.2.2. All patients will remain on treatment until they have received up to a total of 144 weeks of sarilumab exposure calculated from Visit 12. A table to determine when the last on-treatment visit should occur and the weeks between the last on-treatment visit, and the EOT visit based on when the patient was changed to the selected dose regimen is provided in Table 1. After the last on-treatment visit, patients will be scheduled for the EOT visit (Visit 27) and the EOS visit (Visit 28).
- Patients who are enrolled in the third portion with the selected dose regimen will be followed-up as noted in Section 1.2.2.3.

1.2.2.1 *Flow chart for patients who remain on the current dose (selected dose regimen) from the dose-finding portion or recruited directly under the selected dose regimen in the second portion*

	Extension phase (up to 144 weeks of sarilumab exposure from V12)															Post-treatment follow-up (6 weeks)
Visit	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27[a]**	**V28[b]**
Day	**D 113 (±1 or 3)**	**D 141 (±1 or 3)**	**D 169 (±1 or 3)**	**D 225 (±1 or 3)**	**D 281 (±1 or 3)**	**D 337 (±1 or 3)**	**D 421 (±1 or 3)**	**D 505 (±1 or 3)**	**D 589 (±1 or 3)**	**D 673 (±1 or 3)**	**D757 (±1 or 3)**	**D 841 (±1 or 3)**	**D 925 (±1 or 3)**	**D 1009 (±1 or 3)**	**Wk 156/EOT**	**EOS: Wk162/EOT+6 Wks**
Week	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 32**	**Wk 40**	**Wk 48**	**Wk 60**	**Wk 72**	**Wk 84**	**Wk 96**	**Wk 108**	**Wk 120**	**Wk 132**	**Wk 144**		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Home diary/ compliance[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[d]			X			X		X		X		X		X	X	
Call IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tanner stage and menstruation status			X			X		X		X		X		X	X	X
Treatment																
IMP administration[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
IMP dispense	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs																
Temperature, heart rate, blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height (stadiometer)[f]			X			X		X		X		X		X	X	

	Extension phase (up to 144 weeks of sarilumab exposure from V12)															
Visit	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27[a]**	**V28[b]**
Day	**D 113 (±1 or 3)**	**D 141 (±1 or 3)**	**D 169 (±1 or 3)**	**D 225 (±1 or 3)**	**D 281 (±1 or 3)**	**D 337 (±1 or 3)**	**D 421 (±1 or 3)**	**D 505 (±1 or 3)**	**D 589 (±1 or 3)**	**D 673 (±1 or 3)**	**D757 (±1 or 3)**	**D 841 (±1 or 3)**	**D 925 (±1 or 3)**	**D 1009 (±1 or 3)**	**Wk 156/EOT**	**EOS: Wk162/EOT+6 Wks**
Week	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 32**	**Wk 40**	**Wk 48**	**Wk 60**	**Wk 72**	**Wk 84**	**Wk 96**	**Wk 108**	**Wk 120**	**Wk 132**	**Wk 144**		
Efficacy																
JIA ACR core set[g]			X			X		X		X		X		X	X	
JADAS-27[h]			X			X		X		X		X		X	X	
Safety assessment																
AE/SAE recording	|----------															----------|
Tuberculosis risk assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPD tuberculin skin test for patients ≤5 years; QuantiFERON-TB test for patients > 5 years						X				X				X		
Local tolerability	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory testing																
Hematology[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	
Chemistry[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	
Fasting lipids[k]			X			X		X		X					X[k]	
hs-CRP			X			X		X		X		X		X	X[g]	
ESR			X			X		X		X		X		X	X	

	Extension phase (up to 144 weeks of sarilumab exposure from V12)															Post-treatment follow-up (6 weeks)
Visit	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27[a]**	**V28[b]**
Day	**D 113 (±1 or 3)**	**D 141 (±1 or 3)**	**D 169 (±1 or 3)**	**D 225 (±1 or 3)**	**D 281 (±1 or 3)**	**D 337 (±1 or 3)**	**D 421 (±1 or 3)**	**D 505 (±1 or 3)**	**D 589 (±1 or 3)**	**D 673 (±1 or 3)**	**D757 (±1 or 3)**	**D 841 (±1 or 3)**	**D 925 (±1 or 3)**	**D 1009 (±1 or 3)**	**Wk 156/EOT**	**EOS: Wk162/EOT+6 Wks**
Week	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 32**	**Wk 40**	**Wk 48**	**Wk 60**	**Wk 72**	**Wk 84**	**Wk 96**	**Wk 108**	**Wk 120**	**Wk 132**	**Wk 144**		
ANA/anti-dsDNA antibody[l]			X			X		X		X					X[l]	
Local urine pregnancy test for females who are menstruating[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics and ADA																
Serum sarilumab[n]			X			X		X		X		X			X	X
Antibodies to sarilumab[n]			X			X		X		X		X			X	X

Abbreviations: ADA = anti-drug antibody, AE = adverse event, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANA = antinuclear antibodies, ANC = absolute neutrophil counts, AST = aspartate aminotransferase, BP = blood pressure, DNA = deoxyribonucleic acid, D = day, EOT = End-of-Treatment, EOS = End-of-Study, ESR = erythrocyte sedimentation rate, hs-CRP = high sensitivity C-reactive protein, IMP = investigational medicinal product, IVRS = Interactive Voice Response System, JADAS = Juvenile Arthritis Disease Activity Score, JIA ACR = Juvenile Idiopathic Arthritis American College of Rheumatology, PK = pharmacokinetics, PPD = Purified Protein Derivative, SAE = serious adverse event, TB = Tuberculosis, V = visit, Wk/Wks = week, yrs = years.

a. Visit 27 (Week 156) is the study planned End-of-Treatment (EOT) visit. If patients discontinue the study treatment prematurely, EOT will occur 1 week after the last IMP injection for Dose Regimen 3 Cohort and 2 weeks after the last IMP injection for Dose Regimen 1 and 2 Cohorts.
b. Visit 28 (Week162) is the study planned End-of-Study (EOS) visit. If patients discontinue study treatment prematurely, these patients will be asked to return for the End-of-Study (EOS) assessment 6 weeks after the EOT visit (EOT+6 weeks). This EOS visit will be applicable to all the patients in both core treatment phase and extension phase.
c. Home diary for IMP administration to be completed for IMP administered at home.
d. Complete physical examinations will be performed at Visit 15 (week 24), Visit 18 (Week 48), Visit 20 (Week 72), Visit 22 (Week 96), Visit 24 (Week 120), Week 26 (Week 144), and Visit 27 (Week 156) including skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.
e. Investigational medicinal product (IMP) to be administered once every two week for patients in Dose Regimen 1 and 2 Cohorts and once every week for patients in Dose Regimen 3 Cohort. Patients should be monitored for at least 30 minutes after IMP administration for any signs or symptoms of a hypersensitivity reaction. For patients who complete the extension phase, if the selected dose regimen is dosed once every other week (q2w), then the last IMP injection will occur at Week 154; if the selected dose regimen is dosed once a week (qw), then the last IMP injection will occur at Week 155. Patients will have EOT assessment at the Visit 27 (Week 156). For patients who discontinue the study treatment prematurely during the extension phase, it will be preferable to have EOT assessment 2 weeks after the last IMP injection for Dose Regimen 1 and 2 Cohort patients and 1 week after the last IMP injection for Dose Regimen 3 Cohort patients. In case the patient is unable to meet the planned schedule, the EOT visit

will be used for assessment at the next protocol-defined visit after the last IMP injection. Patients will be asked to return to the site for the EOS assessment 6 weeks after the EOT visit. There will be no IMP injection at the Visit 27 (Week 156).

f. Height will be measured using stadiometer at sites during the study.
g. Juvenile Idiopathic Arthritis American College of Rheumatology (JIA ACR) core set includes: global assessment of the severity of disease by the physician, global assessment of overall well-being by the patient or parent, number of joints with active arthritis (defined as swelling within the joint not due to deformity OR limitation of motion and with either pain, tenderness, or both), number of joints with limitation of motion, Childhood Health Assessment Questionnaire (CHAQ), and hs-CRP (2,3,4). If a patient discontinues prematurely before Week 96, hs-CRP must be performed by the central laboratory at EOT.
h. Juvenile Arthritis Disease Activity Score scoring is explained in Section 9.4.2.
i. Hematology (blood should be drawn PRIOR TO drug administration): Hemoglobin, hematocrit, red blood cell (RBC) count and morphology (if RBC count is abnormal), white blood cell (WBC) differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count, absolute neutrophil count (ANC). If a patient discontinues prematurely before Week 96, the test must be performed by the central laboratory at EOT.
j. Chemistry (blood should be drawn BEFORE drug administration): ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and albumin will be tested. Complete chemistry (refer to Section 9.3.4) should be done at Visit 27 EOT (Week 156). If a patient discontinues prematurely before Week 96, the test must be performed by the central laboratory at EOT.
k. Lipids (blood should be drawn BEFORE drug administration): Triglycerides (TG), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol. Patients are required to fast at least 8 hours before the test. At EOT, the test will be performed only for patient who discontinues prematurely before Week 96 and must be performed by the central laboratory.
l. At EOT, the ANA/anti-dsDNA antibody test will be performed only for patient who discontinues prematurely before Week 96 and must be performed by the central laboratory.
m. For females who have commenced menstruating, urine pregnancy tests should be performed prior to exposure to the IMP at each scheduled visit and at the EOT. The urine pregnancy test could be performed locally.
n. Blood samples will be collected PRIOR TO IMP administration on the dosing days during the treatment period. If an SAE occurs in a patient, blood samples should be collected for determination of sarilumab concentration and anti-drug antibody (ADA) assessment at or near the onset and completion of the occurrence of the event, if possible (see Section 9.1).

1.2.2.2 Flow chart for patients enrolled in the dose-finding portion who change to the selected dose regimen (during extension phase)

	Visit (up to a total of 144 weeks of sarilumab exposure from V12)																			Post-treatment follow-up (6 weeks)
Visit	V101	V102	V103	V104	V105	V106	V107	V108	V109	V110	V111	V112	V113	V114	V115	V116	V117	V118	V119	V27[a]	V28[b]
Day at this dose	D 1 (±1 or 3)	D 15 (±1 or 3)	D 29 (±1 or 3)	D 43 (±1 or 3)	D 57 (±1 or 3)	D 85 (±1 or 3)	D 113 (±1 or 3)	D 141 (±1 or 3)	D 169 (±1 or 3)	D 225 (±1 or 3)	D 281 (±1 or 3)	D 337 (±1 or 3)	D 421 (±1 or 3)	D 505 (±1 or 3)	D 589 (±1 or 3)	D 673 (±1 or 3)	D 757 (±1 or 3)	D 841 (±1 or 3)	D 925 (±1 or 3)	EOT	EOS: (EOT +6 Weeks)
Week at this dose	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 48	Wk 60	Wk 72	Wk 84	Wk 96	Wk 108	Wk 120	Wk 132	Check Table 1 for the weeks between patient's last on-treatment visit and EOT	(EOT +6 Weeks)
Tanner stage and menstruation status	X								X			X		X		X		X		X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Home diary for IMP/compliance[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[d]	X			X		X			X			X		X		X		X		X	
Call IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP administration																					
IMP administration[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
IMP dispense	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	Visit (up to a total of 144 weeks of sarilumab exposure from V12)																			Post-treatment follow-up (6 weeks)
Visit	V101	V102	V103	V104	V105	V106	V107	V108	V109	V110	V111	V112	V113	V114	V115	V116	V117	V118	V119	V27[a]	V28[b]
Day at this dose	D 1 (±1 or 3)	D 15 (±1 or 3)	D 29 (±1 or 3)	D 43 (±1 or 3)	D 57 (±1 or 3)	D 85 (±1 or 3)	D 113 (±1 or 3)	D 141 (±1 or 3)	D 169 (±1 or 3)	D 225 (±1 or 3)	D 281 (±1 or 3)	D 337 (±1 or 3)	D 421 (±1 or 3)	D 505 (±1 or 3)	D 589 (±1 or 3)	D 673 (±1 or 3)	D 757 (±1 or 3)	D 841 (±1 or 3)	D 925 (±1 or 3)	EOT	EOS: (EOT +6 Weeks)
Week at this dose	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 48	Wk 60	Wk 72	Wk 84	Wk 96	Wk 108	Wk 120	Wk 132	Check Table 1 for the weeks between patient's last on-treatment visit and EOT	(EOT +6 Weeks)
Vital signs and body measurement																					
Temperature, heart rate, blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height (stadiometer)[f]	X								X			X		X		X		X		X	
Efficacy assessment																					
JIA ACR disease core set[g]	X	X	X	X	X	X			X			X		X		X		X		X	
JADAS-27[h]	X	X	X	X	X	X			X			X		X		X		X		X	
Safety assessment																					
Adverse event/SAE recording	|----------																				----------|
Tuberculosis risk assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Visit (up to a total of 144 weeks of sarilumab exposure from V12)																			Post-treatment follow-up (6 weeks)
Visit	V101	V102	V103	V104	V105	V106	V107	V108	V109	V110	V111	V112	V113	V114	V115	V116	V117	V118	V119	V27[a]	V28[b]
Day at this dose	D 1 (±1 or 3)	D 15 (±1 or 3)	D 29 (±1 or 3)	D 43 (±1 or 3)	D 57 (±1 or 3)	D 85 (±1 or 3)	D 113 (±1 or 3)	D 141 (±1 or 3)	D 169 (±1 or 3)	D 225 (±1 or 3)	D 281 (±1 or 3)	D 337 (±1 or 3)	D 421 (±1 or 3)	D 505 (±1 or 3)	D 589 (±1 or 3)	D 673 (±1 or 3)	D 757 (±1 or 3)	D 841 (±1 or 3)	D 925 (±1 or 3)	EOT	EOS: (EOT +6 Weeks)
Week at this dose	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 48	Wk 60	Wk 72	Wk 84	Wk 96	Wk 108	Wk 120	Wk 132	Check Table 1 for the weeks between patient's last on-treatment visit and EOT	(EOT +6 Weeks)
PPD tuberculin skin test for patients ≤5 yrs; QuantiFERON-TB test for patients >5 yrs	X											X				X					
Local tolerability	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory testing																					
Hematology[i]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	
Chemistry[j]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	
Fasting lipids[k]	X		X			X	X		X			X		X		X				X[k]	
hs-CRP	X	X	X	X	X	X			X			X		X		X		X		X[g]	
ESR	X					X			X			X		X		X		X		X	
ANA/anti-dsDNA antibody[l]	X					X			X			X		X		X				X[l]	

	Visit (up to a total of 144 weeks of sarilumab exposure from V12)																			Post-treatment follow-up (6 weeks)
Visit	V101	V102	V103	V104	V105	V106	V107	V108	V109	V110	V111	V112	V113	V114	V115	V116	V117	V118	V119	V27[a]	V28[b]
Day at this dose	D 1 (±1 or 3)	D 15 (±1 or 3)	D 29 (±1 or 3)	D 43 (±1 or 3)	D 57 (±1 or 3)	D 85 (±1 or 3)	D 113 (±1 or 3)	D 141 (±1 or 3)	D 169 (±1 or 3)	D 225 (±1 or 3)	D 281 (±1 or 3)	D 337 (±1 or 3)	D 421 (±1 or 3)	D 505 (±1 or 3)	D 589 (±1 or 3)	D 673 (±1 or 3)	D 757 (±1 or 3)	D 841 (±1 or 3)	D 925 (±1 or 3)	EOT	EOS: (EOT +6 Weeks)
Week at this dose	Wk 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 48	Wk 60	Wk 72	Wk 84	Wk 96	Wk 108	Wk 120	Wk 132	Check Table 1 for the weeks between patient's last on-treatment visit and EOT	(EOT +6 Weeks)
Local urine pregnancy test for females who are menstruating[m]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics and ADA																					
Serum sarilumab (PK)[n]	X	X	X		X	X			X			X		X		X		X		X	X
Antibodies to sarilumab[n]	X								X			X		X		X		X		X	X

Abbreviations: ADA = anti-drug antibody, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANA = antinuclear antibodies, ANC = absolute neutrophil counts, AST = aspartate aminotransferase, BP = blood pressure, DNA = deoxyribonucleic acid, D = day, EOT = End-of-Treatment, EOS = end-of-study, ESR = erythrocyte sedimentation rate, hs-CRP = high sensitivity C-reactive protein, IMP = investigational medicinal product, IVRS = Interactive voice response system, JADAS = Juvenile Arthritis Disease Activity Score, JIA ACR = Juvenile Idiopathic Arthritis American College of Rheumatology, PK = pharmaco kinetics, PPD = Purified Protein Derivative, SAE = serious adverse event, TB = Tuberculosis, V = visit, Wk = week, yrs = years.

a Visit 27 (Week 156) is the study planned End-of-Treatment (EOT) visit. If patients prematurely discontinue the study, EOT will occur 1 week after the last IMP injection for Dose Regimen 3 Cohort and 2 weeks after the last IMP injection for Dose Regimen 1 and 2 Cohorts.

b Visit 28 (Week 162) is the study planned End-of-Study (EOS) visit. If patients discontinue the study treatment prematurely, these patients will be asked to return for the End-of-Study (EOS) assessment 6 weeks after the EOT visit (EOT+ 6 weeks). This EOS visit will be applicable to all the patients in both the core treatment phase and the extension phase.

c Home diary for IMP administration to be completed for IMP administered at home.

d Complete physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.

e Investigational medicinal product (IMP) to be administered q2w for patients in Dose Regimen 1 and 2 Cohorts and weekly for patients in Dose Regimen 3 Cohort. Patients should be monitored for at least 30 minutes after IMP administration for any signs or symptoms of a hypersensitivity reaction. For patients who complete the extension phase, if the selected dose regimen is dosed once every other week (q2w), then the last IMP injection will occur 2 weeks before EOT if the selected dose regimen is dosed once a week (qw), then the last IMP injection will occur 1 week before EOT. Patients will have EOT assessment at the Visit 27 (Week 156). For patients who prematurely discontinue the study treatment during the extension phase, it will be preferable to have EOT assessment 2 weeks after the last IMP injection for Dose Regimen 1 and 2 Cohort patients and 1 week after the last IMP injection for Dose Regimen 3 Cohort patients. In case the patient is unable to meet the planned schedule, the EOT visit will be used for assessment at the next protocol-defined visit after the last IMP injection. Patients will be asked to return to the site for the EOS assessment 6 weeks after the EOT visit. There will be no IMP injection at the Visit 27 (Week 156).

f Height will be measured using stadiometer at sites during the study.

g Juvenile Idiopathic Arthritis ACR core set (Section 9.4.1) includes: global assessment of the severity of disease by the physician, global assessment of overall well-being by the patient or parent/legal guardian, number of joints with active arthritis defined as swelling within the joint not due to deformity, OR limitation of motion with either pain or tenderness, or both, number of joints with limitation of motion, Childhood Health Assessment Questionnaire (CHAQ), hs-CRP (2,3,4). If a patient discontinues prematurely before Week 96, hs-CRP must be performed by the central laboratory at EOT.

h Juvenile Arthritis Disease Activity Score scoring is explained in Section 9.4.2.

i Hematology (blood should be drawn PRIOR TO drug administration): Hemoglobin, hematocrit, red blood cell (RBC) count and morphology (if RBC count is abnormal), white blood cell (WBC) differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count, absolute neutrophil count (ANC). If a patient discontinues prematurely before Week 96, the test must be performed by the central laboratory at EOT.

j Chemistry (blood should be drawn BEFORE drug administration): ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and albumin will be tested. Complete chemistry (refer to Section 9.3.4) should be done at Visit 27 EOT (Week 156). If a patient discontinues prematurely before Week 96, the test must be performed by the central laboratory at EOT.

k Lipids (blood should be drawn BEFORE drug administration): Triglycerides (TG), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol. Patients are required to fast at least 8 hours before the test. At EOT, the test will be performed only for patient who discontinues prematurely before Week 96 and must be performed by the central laboratory.

l At EOT, the ANA/anti-dsDNA antibody test will be performed only for patient who discontinues prematurely before Week 96 and must be performed by the central laboratory.

m For females who have commenced menstruating, urine pregnancy tests should be performed prior to exposure to the IMP at each visit (except Visits 102 [Week 2] and 103 [Week 6]) and at the EOT. The urine pregnancy test can be performed locally.

n Blood samples will be collected PRIOR TO IMP administration on the dosing days during the treatment period. If an SAE occurs in a patient, blood samples should be collected for determination of sarilumab concentration and anti-drug antibody (ADA) assessment at or near the onset and completion of the occurrence of the event, if possible (see Section 9.1).

Table 1 - Last on-treatment visit prior to EOT visit (V27) for patients who change from a nonselected dose regimen to the selected dose regimen

Visit when the first dose adjustment occurs	Patient's last on-treatment visit prior to V27 (EOT)	Weeks between patient's last on-treatment visit and EOT
V13 (Week 16)	V119 (Week 132)	8 weeks
V14 (Week 20)	V119 (Week 132)	4 weeks
V15 (Week 24)	V118 (Week 120)	12 weeks
V16 (Week 32)	V118 (Week 120)	4 weeks
V17 (Week 40)	V117 (Week 108)	8 weeks
V18 (Week 48)	V116 (Week 96)	12 weeks
V19 (Week 60)	V115 (Week 84)	12 weeks
V20 (Week 72)	V114 (Week 72)	12 weeks
V21 (Week 84)	V113 (Week 60)	12 weeks
V22 (Week 96)	V112 (Week 48)	12 weeks
V23 (Week 108)	V111 (Week 40)	8 weeks
V24 (Week 120)	V109 (Week 24)	12 weeks
V25 (Week 132)	V106 (Week 12)	12 weeks
V26 (Week 144)	V105 (Week 8)	4 weeks

1.2.2.3 Flow chart for patients enrolled directly under the selected dose regimen in the third portion

	Extension phase (up to 84 weeks of sarilumab exposure from V12 for third portion [Portion 3])											Post-treatment follow-up (6 weeks)
Visit	V13[a]	V14[a]	V15	V16[a]	V16.1[b]	V17[a]	V18	V19	V20	V21	V27/EOT[c]	V28/EOS[d]
Day	D 113 (±1 or 3)	D 141 (±1 or 3)	D 169 (±1 or 3)	D 225 (±1 or 3)	D 253 (±1 or 3)	D 281 (±1 or 3)	D 337 (±1 or 3)	D 421 (±1 or 3)	D 505 (±1 or 3)	D 589 (±1 or 3)	Wk 96 for Portion 3	EOT+6Wks: Wk 102 for Portion 3
Week	Wk 16	Wk 20	Wk 24	Wk 32	Wk 36	Wk 40	Wk 48	Wk 60	Wk 72	Wk 84		
Concomitant medication			X		X		X	X	X	X	X	X
Home diary/ compliance[e]			X		X		X	X	X	X	X	
Physical examination[f]			X				X		X		X	
Call IVRS			X		X		X	X	X	X	X	X
Tanner stage and menstruation status			X				X		X		X	X
Treatment												
IMP administration[g]			X		X		X	X	X	X		
IMP dispense			X		X		X	X	X	X		
Vital signs												
Temperature, heart rate, blood pressure			X		X		X	X	X	X	X	X
Weight			X		X		X	X	X	X	X	X
Height (stadiometer)[h]			X				X		X		X	

	Extension phase (up to 84 weeks of sarilumab exposure from V12 for third portion [Portion 3])											Post-treatment follow-up (6 weeks)
Visit	**V13[a]**	**V14[a]**	**V15**	**V16[a]**	**V16.1[b]**	**V17[a]**	**V18**	**V19**	**V20**	**V21**	**V27/EOT[c]**	**V28/EOS[d]**
Day	**D 113 (±1 or 3)**	**D 141 (±1 or 3)**	**D 169 (±1 or 3)**	**D 225 (±1 or 3)**	**D 253 (±1 or 3)**	**D 281 (±1 or 3)**	**D 337 (±1 or 3)**	**D 421 (±1 or 3)**	**D 505 (±1 or 3)**	**D 589 (±1 or 3)**	**Wk 96 for Portion 3**	**EOT+6Wks: Wk 102 for Portion 3**
Week	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 48**	**Wk 60**	**Wk 72**	**Wk 84**		
Efficacy												
JIA ACR core set[i]			X				X		X		X	
JADAS-27[j]			X				X		X		X	
Safety assessment												
AE/SAE recording			X		X		X	X	X	X	X	X
Tuberculosis risk assessment			X		X		X	X	X	X	X	X
PPD tuberculin skin test for patients ≤5 years; QuantiFERON-TB test for patients > 5 years							X					
Local tolerability			X		X		X	X	X	X	X	
Laboratory testing												
Hematology[k]			X		X		X	X	X	X	X[k]	
Chemistry[l]			X		X		X	X	X	X	X[l]	
Fasting lipids[m]			X				X				X[m]	
hs-CRP			X				X		X		X[i]	

	Extension phase (up to 84 weeks of sarilumab exposure from V12 for third portion [Portion 3])											Post-treatment follow-up (6 weeks)
Visit	**V13[a]**	**V14[a]**	**V15**	**V16[a]**	**V16.1[b]**	**V17[a]**	**V18**	**V19**	**V20**	**V21**	**V27/EOT[c]**	**V28/EOS[d]**
Day	**D 113 (±1 or 3)**	**D 141 (±1 or 3)**	**D 169 (±1 or 3)**	**D 225 (±1 or 3)**	**D 253 (±1 or 3)**	**D 281 (±1 or 3)**	**D 337 (±1 or 3)**	**D 421 (±1 or 3)**	**D 505 (±1 or 3)**	**D 589 (±1 or 3)**	**Wk 96 for Portion 3**	**EOT+6Wks: Wk 102 for Portion 3**
Week	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 48**	**Wk 60**	**Wk 72**	**Wk 84**		
ESR			X				X		X		X	
ANA/anti-dsDNA antibody[n]			X				X				X[n]	
Local urine pregnancy test for females who are menstruating[o]			X		X		X	X	X	X	X	
Pharmacokinetics and ADA												
Serum sarilumab[p]			X				X		X		X	X
Antibodies to sarilumab[p]			X				X		X		X	X

Abbreviations: ADA = anti-drug antibody, AE = adverse event, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANA = antinuclear antibodies, ANC = absolute neutrophil counts, AST = aspartate aminotransferase, BP = blood pressure, DNA = deoxyribonucleic acid, D = day, EOT = End-of-Treatment, EOS = End-of-Study, ESR = erythrocyte sedimentation rate, hs-CRP = high sensitivity C-reactive protein, IMP = investigational medicinal product, IVRS = Interactive Voice Response System, JADAS = Juvenile Arthritis Disease Activity Score, JIA ACR = Juvenile Idiopathic Arthritis American College of Rheumatology, PK = pharmacokinetics, PPD = Purified Protein Derivative, SAE = serious adverse event, TB = Tuberculosis, V = visit, Wk/Wks = week, yrs = years.

a Visits 13, 14, 16, and 17 are not applicable for patients in the third portion.

b Visit 16.1 is only applicable for patients in the third portion.

c Visit 27 (Week 96 for third portion) is the study planned End-of-Treatment (EOT) visit. If patients discontinue the study treatment prematurely, EOT will occur 2 weeks after the last IMP injection .

d Visit 28 (Week 102 for third portion) is the study planned End-of-Study (EOS) visit. If patients discontinue study treatment prematurely, these patients will be asked to return for the EOT assessment 2 weeks after the last IMP injection and for the EOS assessment 6 weeks after the EOT visit (EOT+6 weeks). The EOT and EOS visits will be applicable to all the patients prermaturely discontinued in both core treatment phase and extension phase.

e Home diary for IMP administration to be completed for IMP administered at home.

f Complete physical examinations will be performed at Visit 15 (week 24), Visit 18 (Week 48), Visit 20 (Week 72), and Visit 27 (EOT), including skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.

g Investigational medicinal product (IMP) to be administered once every other week (q2w). Patients should be monitored for at least 30 minutes after IMP administration for any signs or symptoms of a hypersensitivity reaction. The last IMP injection will occur at Week 94; then patients will have EOT assessment at the Visit 27 (Week 96 for third portion). There will be no IMP injection at the Visit 27.

h Height will be measured using stadiometer at sites during the study.

i Juvenile Idiopathic Arthritis American College of Rheumatology (JIA ACR) core set includes: global assessment of the severity of disease by the physician, global assessment of overall well-being by the patient or parent, number of joints with active arthritis (defined as swelling within the joint not due to deformity OR limitation of motion and with either pain, tenderness, or both), number of joints with limitation of motion, Childhood Health Assessment Questionnaire (CHAQ), and hs-CRP (2, 3, 4). If a patient discontinues prematurely before Week 48, hs-CRP must be performed by the central laboratory at EOT.

j Juvenile Arthritis Disease Activity Score scoring is explained in Section 9.4.2.

k Hematology (blood should be drawn PRIOR TO drug administration): Hemoglobin, hematocrit, red blood cell (RBC) count and morphology (if RBC count is abnormal), white blood cell (WBC) differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count, absolute neutrophil count (ANC). If a patient discontinues prematurely before Week 48, the test must be performed by the central laboratory at EOT.

l Chemistry (blood should be drawn BEFORE drug administration): ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and albumin will be tested. Complete chemistry (refer to Section 9.3.4) should be done at Visit 27 EOT (Week 96 for third portion). If a patient discontinues prematurely before Week 48, the test must be performed by the central laboratory at EOT.

m Lipids (blood should be drawn BEFORE drug administration): Triglycerides (TG), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol. Patients are required to fast at least 8 hours before the test. At EOT, the test will be performed only for patient who discontinues prematurely before Week 48 and must be performed by the central laboratory.

n At EOT, the ANA/anti-dsDNA antibody test will be performed only for patient who discontinues prematurely before Week 48 and must be performed by the central laboratory.

o For females who have commenced menstruating, urine pregnancy tests should be performed prior to exposure to the IMP at each scheduled visit and at the EOT. The urine pregnancy test could be performed locally.

p Blood samples will be collected PRIOR TO IMP administration on the dosing days during the treatment period. If an SAE occurs in a patient, blood samples should be collected for determination of sarilumab concentration and anti-drug antibody (ADA) assessment at or near the onset and completion of the occurrence of the event, if possible (see Section 9.1).

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3 LIST OF ABBREVIATIONS

ACR:	American College of Rheumatology response criteria
ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event(s) of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANA:	antinuclear antibody
ANC:	absolute neutrophil count
anti-dsDNA:	anti-double stranded DNA
AST:	aspartate aminotransferase
BP:	blood pressure
BUN:	blood urea nitrogen
CHAQ:	Childhood Health Assessment Questionnaire
COX-2:	cyclo-oxygenase-2 inhibitors
CRF:	case report form
CRP:	C-reactive protein
CSR:	clinical study report
CYP:	cytochrome
DMARD:	disease modifying antirheumatic drug
DMC:	Data Monitoring Committee
DNA:	deoxyribonucleic acid
EBV:	Epstein-Barr virus
e-CRF:	electronic case report form
EOS:	end-of-study
EOT:	end-of-treatment
ESR:	erythrocyte sedimentation rate
FDA:	Food and Drug Administration
GCP:	good clinical practice
HAQ-DI:	Health Assessment Questionnaire Disability Index
HBc-Ab:	hepatitis B core antibody
HIV:	human immunodeficiency virus
HR:	heart rate
hs-CRP:	high sensitivity C-reactive protein
ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent ethics committee
IgG:	immunoglobulin G
IL-6:	Interleukin 6
IL-6R:	IL-6 receptor
ILAR:	international league of associations for rheumatology
IMP:	investigational medicinal product

IRB:	Institutional Review Board
IVRS:	interactive voice response system
IWRS:	interactive web response system
JADAS:	Juvenile Arthritis Disease Activity Score
JAK:	Janus kinase
JIA:	juvenile idiopathic arthritis
LLOQ:	lower limit of quantification
mTSS:	modified total sharp score
MTX:	methotrexate
NIMP:	noninvestigational medicinal product
NSAID:	Non-steroidal anti-inflammatory drugs
oJIA:	oligoarticular juvenile idiopathic arthritis
pcJIA:	polyarticular course of juvenile idiopathic arthritis
PD:	pharmacodynamic
PK:	pharmacokinetic
PopPK:	Population pharmacokinetic
PPD:	Purified Protein Derivative
q2w:	once every other week
qw:	once a week
RA:	rheumatoid arthritis
RF:	rheumatoid factor
SAE:	serious adverse event
SC:	subcutaneous
sIL-6R:	soluble interleukin-6 receptor
SUSAR:	suspected unexpected serious adverse reaction
TEAE:	treatment-emergent adverse event
TNF:	Tumor necrosis factor
ULN:	upper limit of normal
VAS:	visual analogue scale

4 INTRODUCTION

4.1 INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood. It is defined by the International League of Associations for Rheumatology (ILAR) as arthritis of unknown etiology with onset before 16 years of age that persists for at least 6 weeks with other known conditions excluded (2,3,5,6,7). Juvenile idiopathic arthritis (JIA) comprises 7 subtypes categorized by age of onset, range, and disease characteristics in the first 6 months after onset as defined by the ILAR in 2001 (2).

Polyarticular course juvenile idiopathic arthritis (pcJIA), a subtype of JIA, affects at least 5 joints. Both large and small joints can be involved, and often in symmetric bilateral distribution, and often involving weight-bearing joints and small joints in the hands. Low grade fevers can accompany the arthritis. Presence of rheumatoid factor (RF) differentiates the 2 forms of pcJIA: RF-positive and RF-negative pcJIA:

Rheumatoid factor (RF)-positive pcJIA represents a relatively small proportion of all children and adolescents with JIA (3%-5%) but it is the only JIA subgroup resembling adult rheumatoid arthritis (RA), a deforming symmetrical polyarthritis, due to chronic synovial inflammation, articular cartilage loss and erosion of juxta-articular bone. Features of RF-positive pcJIA are the mean onset at age of 12 to 14 years, the marked female gender predominance (13:1 female/male ratio), symmetrical involvement of small and large joints, production of polyclonal IgM RF or antiCCP antibodies, genetic susceptibility (association with the HLA-DR4 allele), a clinical course marked by normocytic chronic anemia (reticuloendothelial block), and acute phase proteins (elevated ESR and C-reactive protein [CRP]) that rarely remits spontaneously, as well as elevated white blood cell count. The association with firm, mobile and nonpainful rheumatoid nodule formation is possible but rare. Laboratory findings are expected to be more severe than those associated with oligoarthritis. Long-term sequelae include joint subluxation (wrists and thumbs), joint contractures (proximal and distal interphalangeals, bone overgrowth of proximal interphalangeals, and finger deformities (eg, swan-neck or boutonniere deformities). Asymptomatic arthritis of the cervical spine, associated with decreased extension, can lead to subluxation, typically of C2 vertebrae on C3 and fusion of the posterior vertebral elements. Arthritis of the temporal-mandibular joint may also be asymptomatic and lead to micrognathia (2).

Rheumatoid factor (RF)-negative pcJIA presents at a younger age (in late childhood, 7 to 9 years) than RF-positive pcJIA and represents 11 to 28% of all children and adolescents with JIA. It may not be as destructive and persistent as RF-positive disease but does, by definition, involve 5 or more joints. Radiologic changes in RF-negative disease occur later than in RF-positive disease. Severe limitations in motion are usually accompanied by muscle weakness and decreased physical function.

Oligoarticular JIA (oJIA) (5,6,7), another subtype of JIA, is the most common subtype of juvenile arthritis, representing approximately 50% of all patients with JIA in the US and Western Europe.

Onset ranges from 1 to 5 years and peaks at 2 to 3 years. It is defined as an aseptic inflammatory synovitis that affects generally up to 4 joints (typically larger joints, such as knees, ankles, wrists) and is not associated with constitutional findings such as fever, weight loss, fatigue or systemic signs of inflammation. Nevertheless, if greater than 4 joints become affected after the first 6 months of disease, it is designated as extended oligoarthritis in contrast to persistent oJIA that features only up to 4 joints throughout the course of the disease. Children are often well-appearing despite ambulating with a limp. Oligoarticular JIA carries a risk for developing chronic anterior uveitis, especially when antinuclear antibodies (ANA) are present and disease onset is in early childhood. It is typically asymptomatic at onset and requires screening by ophthalmologic slit lamp examination. Chronic arthritis in a knee or ankle may lead to overgrowth of that limb with subsequent leg length discrepancy. Muscle atrophy, often of extensor muscles (eg, vastus lateralis, quadriceps when knee affected) and/or flexion contractures in the knees and, less commonly, the wrists are found.

Please refer to Appendix A for Subclassification of RF-negative, RF-positive, polyarticular and oJIA. For the purpose of this study, extended oligoarticular, RF-positive and RF-negative polyarticular JIA will be referred to as polyarticularcourse (pcJIA).

Interleukin 6 (IL-6) is a key cytokine involved in the pathogenesis of RA and JIA causing inflammation, and joint destruction (8,9,10,11). The relevance of elevated IL-6 levels to disease mechanisms of polyarticular JIA (RF- and RF+ has been well documented in the medical-scientific literature (12). Inhibition of IL-6 signaling through blockade of the IL-6 receptor (IL-6R) was first demonstrated to be effective in pcJIA by tocilizumab, an intravenously administered, humanized monoclonal antibody (mAb) to the IL-6R (13,14). In the pcJIA studies that led to the approval of tocilizumab in this indication, the safety profile of tocilizumab appeared to be similar to that of the adult RA population.

Sarilumab is a recombinant human monoclonal antibody of the immunoglobulin G (IgG) isotype targeting the IL-6R α subunit (IL-6Rα). Sarilumab blinds the human IL-6Rα and has been demonstrated to inhibit IL-6 signaling. [redacted]

Sarilumab may become an effective and safe therapeutic option for patients suffering from pcJIA. This study will evaluate the efficacy, safety, and pharmacokinetic (PK), pharmacodynamic (PD) profiles of different doses of sarilumab administered to patients with pcJIA.

4.2 CLINICAL PROGRAM IN ADULT RHEUMATOID ARTHRITIS (RA)

The efficacy and safety of sarilumab, whether or not added to a nonbiologic disease modifying antirheumatic drug (DMARD), have been evaluated in adult patients with active RA. The dose regimens selected for the Phase 3 program in adults were 150 mg once every other week (q2w) and 200 mg q2w. These selected dose regimens added to methotrexate (MTX) in patients who are MTX inadequate responders, 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 response criteria, ACR20, physical function (Health

Assessment Questionnaire Disability Index, [HAQ-DI]), and radiographic progression (Van der Heijde modified total Sharp score, vdH-mTSS]) in the double-blind, placebo-controlled, SARIL-RA-MOBILITY (EFC11072) study:

- Improvement in signs and symptoms of RA at 24 weeks as measured by the ACR20 (proportion of patients achieving an ACR20 response: 58.0% for the sarilumab 150 mg q2w group, 66% for the sarilumab 200 mg q2w group, and 33% for the placebo group).
- Improvement in physical function, as measured by the change from baseline in the HAQ-DI at Week 16 (-0.54 for the sarilumab 150 mg q2w group, -0.58 for the sarilumab 200 mg q2w group, and -0.30 for the placebo group).
- Inhibition of progression of structural damage at Week 52, as measured by the change from baseline in them TSS (0.90 for the sarilumab 150 mg q2w group, 0.25 for the sarilumab 200 mg q2w group, and 2.78 for the placebo group).

The improvements in the ACR20 response and HAQ-DI were maintained up to Week 52 (End-of-Treatment [EOT]). The sarilumab 200 mg q2w group had a reduction of approximately 90% in the radiographic progression that was assessed by the mTSS, compared to the placebo group.

Another phase 3 efficacy and safety study, SARIL-RA-TARGET (EFC10832) enrolled total 546 patients into three treatment groups, placebo (181), sarilumab 150 mg q2w (181) and sarilumab 200 mg q2w (184). Both doses of sarilumab showed clinically relevant and statistically significant improvements compared with placebo in 2 co-primary endpoints:

- Improvement in signs and symptoms of RA at 24 weeks as measured by the ACR20 response at Week 24 (the proportion of patients achieving an ACR20 response: 56% for the sarilumab 150 mg q2w group, 61% for the sarilumab 200 mg q2w group, and 34% for the placebo group $p<0.0001$)
- Improvement in physical function, as measured by the change from baseline in HAQ-DI at Week 12. The results demonstrated statistically significant difference in favor of sarilumab in HAQ-DI change from baseline at Week 12 in the sarilumab 200 mg q2w and 150 mg q2w dose groups (-0.21 and -0.20 units), compared to placebo, with p-values of 0.0004 and 0.0007, respectively.

The safety profile in SARIL-RA-MOBILITY was consistent with the anticipated effects of IL-6 inhibition. There was a higher incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to withdrawal in the sarilumab treatment groups compared to placebo. The incidences of treatment-emergent SAEs in the sarilumab treatment groups were higher compared to placebo (for 100 patient years, there were 18.7, 16.8, and 12.9 events in the 200 mg q2w, 150 mg q2w, and placebo treatment groups, respectively). Infections were the most frequently reported SAEs (for 100 patient years, there were 4.7, 3.0, and 3.3 patients and 6.0, 3.8, and 3.9 events in the 200 mg q2w, 150 mg q2w, and placebo treatment groups, respectively), generally involving the respiratory tract or skin/soft tissue. In the sarilumab treated groups compared to placebo, there were decreases in neutrophil count, elevation in alanine aminotransferase (ALT), elevation in serum LDL-cholesterol and injection site reactions (ie, erythema, pain). 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 anti-drug antibody (ADA)-positive and ADA-negative.

The safety profile of sarilumab observed in SARIL-RA-TARGET (EFC10832) was consistent with that observed for MOBILITY and other RA studies in the phase 3 registration program.

Based on the safety profile of tocilizumab (an approved IL-6R inhibitor) and other biological DMARDs, potential important risks to be considered with sarilumab administration are tuberculosis and clinically significant opportunistic infections, complications of diverticulitis/gastrointestinal perforations, anaphylaxis, clinical consequences of immunogenicity, clinical consequences of thrombocytopenia, malignancy, and demyelinating disorders. In addition, clinical consequences of laboratory abnormalities which may occur due to sarilumab administration (eg, serious infection secondary to neutropenia) are considered an important potential risk.

Based on the experience to date from the sarilumab clinical development program, the potential important risks associated with sarilumab administration are non-opportunistic infections, neutropenia, elevation in lipids, elevation in liver transaminase, and injection site reactions (ie, erythema, pain).

From the results of the sarilumab RA development program in adult patients, the two selected dose regimens of sarilumab for the phase 3 program were recognized efficacious with an acceptable safety profile by Health Agencies worldwide including the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMA) in Europe who approved them for the treatment of adult RA. The recommended dose regimen in US and EU is 200 mg q2w that is to be reduced to 150 mg q2w for management of neutropenia, thrombocytopenia, and elevated liver enzymes. These 3 dose regimens served as an appropriate reference for the evaluation of sarilumab in pediatric patients with polyarticular course and systemic juvenile idiopathic arthritis (pcJIA and sJIA). For complete information regarding the preclinical and clinical evaluation of sarilumab to date, see the Clinical Investigator's Brochure (Edition 13, 28 February 2017).

4.3 STUDY RATIONALE

4.3.1 Choice of the dose regimen

This study targets children and adolescents aged 2 to 17 (or country specified age requirement) with pcJIA, a JIA subset that resembles adult RA. In this pediatric population, 3 dose regimens of sarilumab are planned to be tested.

[redacted] Population pharmacokinetic (PopPK) analyses in adult RA patients showed that age, gender, and race did not affect the PKs of sarilumab. Weight was found to impact sarilumab exposure with higher exposure observed in patients with lower weight.

Due to differential growth rates in young children, there is a much larger variability in body size for children than for adults. In addition, since body weight has an important effect on the clearance of monoclonal antibodies; a weight-adjusted dosage may be required for patients of different weights in order to achieve relatively comparable drug exposure from a recommended fixed dose regimen in adults.

[redacted]

Sarilumab at doses of 150 mg q2w, 200 mg q2w, and 150 mg once a week (qw) all demonstrated improvements in endpoints of RA disease activity with the safety profile anticipated for an IL-6R antagonist. The published literature suggests that exposures that are efficacious in adult RA are likely to be efficacious in pcJIA. Therefore, Dose 1 for this pcJIA study has been chosen to yield an exposure similar to 150 mg q2w (the lowest efficacious dose) observed in the adult RA program. Dose 2, the second dose level to be evaluated in this study, has been predicted to achieve an exposure comparable to the sarilumab 200 mg q2w dose observed in the adult RA program. Dose 3, the third dose level to be evaluated in this study, has been predicted to achieve an exposure comparable to the sarilumab 150 mg qw dose observed in the adult RA program, the highest dose level tested in the adult program that also demonstrated better improvement in signs and symptoms of RA compared to placebo and had an acceptable safety profile.

The approximate equivalents of a 150 mg or 200 mg dose for a 75 kg adult RA patient are 2 mg/kg or 3 mg/kg, respectively. [redacted]. The PK target for the pediatric population was comparable exposure to that observed in adult RA patients for dosing regimens of 150 mg q2w or 200 mg q2w. [redacted]

In addition, in sarilumab program in adult RA, the dose regimen that provided the highest exposure, ie, 150 mg qw was received by more than 300 patients including about 30% patients for one year.

4.3.2 Study design

This multi-center Phase 2b study has been designed to determine the appropriate dose and regimen for adequate treatment of patients with pcJIA disease based on PK, PD, safety, and efficacy evaluation of the 3 sarilumab dose regimens tested in the study. With the ethical concern to not expose these children to a noneffective dose for a too long period due to the potential severity and chronicity of the disease, the open-label sequential ascending repeat-dose design was preferred to a double-blind, placebo-controlled, parallel arms design.

The 12-week core treatment phase of the study comprises 3 portions. The first portion is a dose-finding portion that follows a multiple ascending dose design. Within a dose regimen cohort, treatment will initiate in the higher weight group A (≥30 kg and ≤60 kg), as these children are older. Dosing will commence in the lower weight group B (<30 kg and ≥10 kg) after reviewing PK, PD, efficacy, and safety data from the first dose regimen tested in group A. The duration of the core treatment period (12 weeks) is consistent with the generally accepted time period required to assess the clinical effect of a biological therapy for JIA.

The proposed stepwise evaluation of different sarilumab doses in the dose-finding portion of the 12-week core treatment phase of the study, starting with the lowest effective dose that had an acceptable safety profile observed in the adult RA program, is appropriate to ensure a balance of the potential efficacy and safety considerations for the first dose of sarilumab to be assessed in the pediatric population in this study. This adaptive sequential design will minimize the exposure of children to an ineffective or unsafe dose with rules for prematurely stopping a dose regimen cohort for lack of efficacy and the stepwise approach for evaluating each dose regimen cohort before allowing next one. The third dose may be evaluated in this study, after review of the PK, PD, and clinical safety/efficacy data from the prior dose regimen cohorts, if it is determined that another dose regimen may allow for further optimization of the benefit-risk balance for this study population.

After completing the investigation of the ascending dose regimen cohorts in the dose-finding portion of the 12-week core treatment phase, one dose regimen will be selected by the Dose Escalation Committee (DEC) and additional patients will be enrolled at the selected dose regimen (second portion of the core treatment phase) to obtain 18 evaluable patients per weight group with that selected dose regimen in order to provide sufficient precision for PK parameters and PK-PD relationship assessments. Those patients will undergo the same assessments as patients recruited in the dose-finding portion.

Additionally, after completing the enrollment of dose-finding and second portions, a third portion where approximately 28 additional patients will be enrolled directly to the selected dose regimen to achieve a total of approximately 100 treated patients for the entire study as per a health authority recommendation. These patients will undergo the same on-site visits during the 12-week core treatment phase as patients recruited in the dose-finding and second portions; however, the patients in the third portion will not have the sarilumab PK sampling visits between Baseline and Week 2.

An additional treatment period in the extension phase will allow collection of long-term safety and clinical response data for sarilumab in pcJIA patients. This extension phase is up to 144 weeks for patients enrolled in the dose-finding and second portions and up to 84 weeks for patients enrolled in the third portion. Patients enrolled in the dose-finding portion who are already in the extension phase at time of dose regimen selection and who did not receive the selected dose regimen will have their dose regimen adjusted to the selected dose.

To minimize the amount of blood collected, Group B patient (<30 kg and ≥10 kg) in the dose-finding and second portions will be randomized to 1 of 2 different sarilumab PK sample collection schedules. The PK analyses will integrate these sampling schedules to describe the PK profile of sarilumab (see Section 9.1). No PK sample collection is planned between Baseline and Week 2 for patients enrolled in the third portion. Total volume of blood withdraw for the study will not exceed 3% of the total blood volume during a period of 4 weeks and not exceed 1% of the total blood volume at any single time (16).

Furthermore, the planned frequent assessments control risk to study participants.

Lastly, the post-treatment follow-up period of 6 weeks after the last treatment visit for TEAEs, sarilumab PK and PD assessments is appropriate taking into account the observed PK profiles in the adult RA program.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to describe the PK profile of sarilumab in patients aged 2 to 17 years with pcJIA in order to identify the dose and regimen for adequate treatment of this population.

5.2 SECONDARY

The secondary objectives are to describe:

- The PD profile and the efficacy of sarilumab in patients with pcJIA.
- The long-term safety of sarilumab in patients with pcJIA.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

DRI13925 is a multinational, multicenter, open-label, 2-phase study in children and adolescents, aged 2 to 17 years (or country specified age requirement), with pcJIA who have inadequate response to or who are intolerant to standard therapy and who will receive SC injections of sarilumab administrated q2w or qw. The 2 phases are as follows:

1. **A 12-week core treatment phase, split into 3 portions:**

- A first sequential, ascending dose-cohort, dose-finding portion in which up to 3 dose regimens will be investigated in two weight groups: patients ≥30 kg and ≤60 kg (Group A) and patients <30 kg and ≥10 kg (Group B) in 6 evaluable patients per dose and weight group (around 36 patients in total). Patient enrollment will be staggered by weight group and dose regimen, starting with Group A (≥30 kg and ≤60 kg) and Dose Regimen 1 Cohort.
- A subsequent portion where approximately 24 additional patients (12 in each weight group: ≥30 kg [Group A] and patients <30 kg and ≥10 kg [Group B]) will be enrolled directly to the selected dose regimen (identified based on the aggregate data from patients enrolled in the dose-finding portion) to achieve a total of 18 evaluable patients per weight group at this selected dose regimen. These patients will undergo the same 12-week core treatment assessments as patients recruited during the dose-finding portion.
- A third portion where approximately 28 additional patients (a cap of 70% in each weight group: patients ≥30 kg [Group A] and patients <30 kg and ≥10 kg [Group B]) will be enrolled directly to the selected dose regimen to achieve a total of approximately 100 treated patients for the entire study. These patients will undergo the same on-site visits during the 12-week core treatment phase as patients recruited in the dose-finding and second portions; however, the patients in the third portion will not have the sarilumab PK sampling visits between Baseline and Week 2.

The 12-week core treatment phase is from Visit 2 (Baseline-Week 0) to the time that Visit 12 investigational medicinal product (IMP) is administrated. During the 12-week core treatment phase, for the dose-finding and second portions, patients in the lower weight group (Group B: <30 kg and ≥10 kg) will be randomly assigned to the following sarilumab PK sampling Schedule 1 or 2 (Section 9.1.1) in order to minimize the amount of blood withdrawn and the number of visits while maintaining the evaluation of the primary endpoint:

- Schedule 1: Baseline, Day 3, Day 8, Week 2, Week 4, Week 8, and Week 12
- Schedule 2: Baseline, Day 5, Day 12, Week 2, Week 4, Week 8, and Week 12.

2. An extension phase:

- A 144-week extension for patients enrolled in the dose-finding and second portions: The IMP at Visit 12 is considered as the first IMP for the extension phase. Only patients who have reached a JIA ACR30 response at Visit 12 (Week 12) will be permitted to continue in the extension phase. Patients will continue on the same dose regimen of sarilumab they were assigned to receive in the 12-week core treatment phase of the study until the selected dose regimen is determined. Once the dose regimen is selected, patients who were not already on this dose regimen will have their dose regimen adjusted to the selected dose regimen and will follow a new visit schedule with more frequent monitoring (for PK, safety, and efficacy) for the first 12 weeks compared to those patients who do not have dose regimen adjusted (Section 1.2.2.2).
- An 84-week extension for patients enrolled in the third portion. The IMP at Visit 12 is considered as the first IMP for the extension phase.

3. End-of-Treatment (EOT) and End-of-Study (EOS):

- For patients enrolled in the dose-finding and second portions: Patients who discontinue the study treatment prematurely will be assessed using the procedure for the EOT at Visit 27. These patients will be asked to return for the end-of-study (EOS) assessment 6 weeks after the EOT visit (EOT + 6 weeks). For patients who discontinue the study treatment during the 12-week core treatment phase, there will be an additional sarilumab PK assessment 2 weeks after the EOT visit (EOT + 2 weeks) and IL-6 and soluble interleukin-6 receptor (sIL-6R) will be measured at EOT visit. These patients will be asked to perform all the protocol scheduled visits and assessments except sarilumab administration until Visit 12.
- For patients enrolled in the third portion: Patients who discontinue the study treatment prematurely will be assessed using the procedure for the EOT at Visit 27 and will be asked to return for the EOS assessment 6 weeks after the EOT visit (EOT + 6 weeks). For patients who prematurely discontinue the study treatment during the 12-week core treatment phase, the IL-6 and sIL-6R will be measured at the EOT visit, and they will be asked to participate in all the protocol scheduled visits and assessments except sarilumab administration until Visit 12.

6.1.1 Tested dose regimens

For each weight group, to the 3 sequential ascending dose regimens to be tested were defined based on PK modeling with the following rationale:

- Dose Regimen 1: dose targeting PK exposures similar to sarilumab 150 mg q2w, the lowest effective dose in adult patients with RA
- Dose Regimen 2: dose with targeted PK exposures similar to sarilumab 200 mg q2w in adult patients with RA
- Dose Regimen 3: dose targeting PK exposures similar to sarilumab 150 mg qw, which yielded the highest exposures in chronic dosing studies in adult patients with RA.

Table 2 - Dose by body weight and dose regimen

Body weight	Dose Regimen 1	Dose Regimen 2	Dose Regimen 3
Group A ≥30 kg and ≤60 kg	2 mg/kg q2w (6 patients)	3 mg/kg q2w (6 patients)	2 mg/kg qw (6 patients)
Group B <30 kg and ≥10 kg	2.5 mg/kg q2w (6 patients)	4 mg/kg q2w (6 patients)	2.5 mg/kg qw (6 patients)

Abbreviations: qw = once every week, q2w = once every other week.

The dose (mg) to be administered to patients will be calculated at the Baseline. The dose and corresponding volume of drug product will remain the same throughout the course of the 12- week core treatment phase of the trial regardless of change in patient's body weight. In the extension phase, the patient's weight will be measured at each visit and the dose will be adapted to the increase of weight only if the calculation shows a need for dose increase. The dose will be capped at 150 mg for Dose Regimen 1 and 3, and 200 mg for Dose Regimen 2, respectively. Volumes of sarilumab to be injected for Dose Regimens 1 to 3 are presented in Appendix B.

6.1.2 Rules for the stepwise approach

6.1.2.1 For permitting enrollment into Dose Regimen 1 Cohort for Group B (<30 kg and ≥10 kg)

Enrollment in the first Dose Regimen Cohort Group B (<30 kg and ≥10 kg), will initiate after the review of safety, efficacy, and available PK/PD and efficacy data for a minimum of 3 out of the 6 patients planned in that same tested Dose Regimen Cohort in Group A (≥30 kg and ≤60 kg) who have completed at least 4 weeks of study treatment.

6.1.2.2 For escalating the dose in a group

The decision to initiate the next dose regimen cohort in the same weight group will be taken by the DEC and will depend on the data review of at least 6 weeks of efficacy and safety data as well as the available PK and PD data for a minimum of 3 patients out of the 6 from the current dose regimen cohort in the weight Group A.

Dose Regimen 3 Cohort in weight Group B will be initiated based on DEC decision after review of efficacy and safety as well as the available PK, and PD data from Dose Regimen 1 and 2 Cohorts of Groups A and B.

6.1.2.3 For prematurely stopping enrollment in a dose regimen cohort weight group

A dose regimen cohort for a weight group may be prematurely terminated after review of the 6-week data for at least 3 patients out of the 6 planned to be enrolled in that dose regimen cohort weight group if none of these patients have reached JIA ACR 30 response. The decision will be taken by the DEC who will consider all available efficacy, safety, PK, and PD data and confirm the current dose regimen to be ineffective.

If a dose is declared to be ineffective, no additional patients will be enrolled in that dose regimen cohort weight group and, if there is no major safety concern, the next dose regimen cohort will be initiated immediately. Any patient that has been included in that dose regimen cohort weight group will have to discontinue from the study treatment and receive the standard of care treatment as per the Investigator's clinical judgment.

6.1.2.4 Rules for dose regimen selection

The decision about the selected dose regimen will be made by the DEC after review of sufficient Week 12 PK, PD, efficacy, and safety data from the patients enrolled in the dose-finding portion of the study.

6.2 STUDY COMMITTEES

6.2.1 Data Monitoring Committee review for ensuring patients' safety

The Data Monitoring Committee (DMC) will be composed of independent pediatric rheumatologists who are not participants in the sarilumab pediatric clinical studies, are not sponsor employees, and do not have any conflict of interest with regard to study outcomes. The DMC will monitor patient safety by conducting formal reviews of accumulated safety data. The DMC will also review efficacy, PK, and PD data to evaluate the benefit-risk profile of sarilumab. The DMC members' responsibilities and the process for data review are described in the DMC charter.

6.2.2 Dose Escalation Committee review for dose selection

The DEC is composed of sponsor representatives who will review the study data on a continuous basis as well as between dose regimen cohorts. The DEC will decide the appropriate course of action for the study, such as continuation to the next dose regimen cohort or modifications to the protocol.

DEC member responsibilities and the process for dose escalation decisions are described in the DEC charter.

6.3 DURATION OF STUDY PARTICIPATION

6.3.1 Duration of study participation for each patient

Total duration of study (per patient) is expected to be up to 166 weeks for patients enrolled in the dose-finding and second portions and up to 106 weeks for patients enrolled in the third portion:

- Up to 4 weeks + 3 days screening (up to 31 days)
- 12-week core treatment phase

- Up to 144-week extension phase for patients enrolled in the dose-finding and second portions and up to 84-week extension phase for patients enrolled in the third portion
- 6-week post-treatment follow-up.

For all visits, a time frame of ±3 days for Dose Regimen 1 and 2 Cohorts and ±1 day for Dose Regimen 3 Cohort is acceptable using Day 1 as reference except for

- For Visit 3 (Day 3), Visit 4 (Day 5) and Visit 5 (Day 8), no visit window is allowed where PK sampling occurs
- Visit 6 (Day 12) ±1 day for all applicabledose regimen cohorts
- Visit 7 (Week 2) ±1 day for all dose regimen cohorts
- Visit 8 (Week 4) ±2 days for Dose Regimen 1 and 2 Cohorts and ±1 day for Dose Regimen 3 Cohort.

6.3.2 Determination of end of clinical trial (all patients)

The end of the clinical trial in all participating sites is reached when the last patient last visit is completed per protocol. The last patient last visit will occur at Visit 28/EOS for all patients who complete the open-label extension period of the study.

6.4 INTERIM ANALYSIS

Refer to Section 11.5 for details on interim analyses.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Male and female patients aged ≥2 and ≤17 years (or country specified age requirement) at the time of the Screening visit

I 02. Diagnosis of RF-negative or RF-positive polyarticular JIA subtype or oJIA subtype according to the ILAR 2001 JIA Classification Criteria (2) with at least 5 active joints per ACR definition for "active arthritis" at Screening (Appendix A)

I 03. Patient with an inadequate response to current treatment and considered as a candidate for a biologic DMARD as per Investigator's judgment

I 04. The patient who has reached the legal age of consent, or the parent(s) or the legal guardian(s) sign and date the Ethic Committee approved written informed consent. The patient's assent should be obtained based on local guidelines and the patient's maturity and intellectual capabilities of understanding the study associated information. In cases involving emancipated or mature minors with adequate decision-making capacity, or when otherwise permitted by law, a signed informed consent will be obtained directly from the parent(s) or the legal guardian(s).

7.2 EXCLUSION CRITERIA

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

7.2.1 Exclusion criteria related to study methodology

E 01. Body weight <10 kg or >60 kg for patients enrolled in the 3 ascending dose regimen cohorts, then body weight <10 kg for patients subsequently enrolled at the selected dose regimen cohorts

E 02. Wheelchair-bound or bed-ridden

E 03. Diagnosis of JIA subtypes except polyarticular RF-positive (RF+) or RF-negative (RF-) JIA or extended oJIA

E 04. If non-steroidal anti-inflammatory drugs (NSAIDs) (including cyclo-oxygenase-2 inhibitors [COX-2]) taken, dose stable for less than 2 weeks prior to the Baseline visit and/or dosing prescribed outside of approved label

E 05. If nonbiologic DMARD taken, dose stable for less than 6 weeks prior to the Baseline visit or at a dose exceeding the recommended dose as per local labeling

E 06. If oral glucocorticoid taken, dose stable for <2 weeks or dose exceeding equivalent prednisone dose 0.5 mg/kg/day (or 30 mg/day) within 2 weeks prior to Baseline

E 07. Use of parenteral or intra-articular glucocorticoid injection within 4 weeks prior to Baseline

E 08. Prior treatment with anti-IL-6 or IL-6R antagonist therapies, including but not limited to tocilizumab or sarilumab

E 09. Treatment with any biologic treatment for pcJIA within 5 half-lives prior to the first dose of sarilumab as follows (the required off-treatment periods and procedures may vary according to local requirements):

- Etanercept: within 4 weeks
- Infliximab: within 8 weeks
- Adalimumab: within 15 weeks
- Anakinra: within 2 days
- Canakinumab: within 19 weeks
- Abatacept: within 10 weeks
- Rituximab or other cell-depleting agent: within 16 weeks or until total lymphocyte count and CD 19+ lymphocyte count are normalized, whichever is longer
- Intravenous Ig: within 15 weeks

E 10. Treatment with a Janus kinase (JAK) inhibitor within 4 weeks prior to the first dose of sarilumab; and treatment with growth hormone within 4 weeks prior to the first dose of sarilumab (the required off-treatment periods and procedures may vary according to local requirements)

E 11. Treatment with any investigational biologic or non-biologic product (Appendix J) within 8 weeks or 5 half-lives prior to Baseline, whichever is longer

E 12. Lipid lowering drug stable for less than 6 weeks prior to Screening

E 13. Exclusion related to tuberculosis:

- Active TB or a history of incompletely treated TB
- Purified Protein Derivative (PPD) or QuantiFERON-TB positive patients (no active disease) are excluded from the study unless the following conditions are met:
  - It is documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and / or infectious disease specialist
  - No evidence of active TB infection indicated by the chest radiograph performed according to local guidance for the screening of TB infection prior to the study

- Suspected extrapulmonary TB infection
- Patients at high risk of contracting TB, such as close contact with individual with active or latent TB

E 14. Exclusion criteria related to past or current infection other than tuberculosis:

- History of invasive opportunistic infections, including but not limited to histoplasmosis, listeriosis, coccidioidomycosis, candidiasis, pneumocystis jirovecii, aspergillosis despite resolution, or John Cunningham virus (progressive multifocal leukoencephalopathy [PML]).
- History of recurrent or active herpes zoster or reactivation or new onset of Epstein-Barr virus (EBV) or positive test for EBV within 2 months of the screening (or at the Screening visit)
- Diagnosed nontuberculous mycobacterial infection based on clinical, radiological and microbiological evidence within 2 months of the screening (or at the Screening visit)
- History of prior articular or prosthetic joint infection
- Fever (>38°C), or chronic, persistent, or recurring infection(s) requiring active treatment with antibiotics, antivirals, or antifungals within 4 weeks prior to the Screening visit or other frequent recurrent infections deemed unacceptable, as per the Investigator judgment
- Previous or at the Screening: hepatitis B surface antigen (HBs-Ag) positive, or total hepatitis B core antibody (HBc-Ab) positive; previous or at the Screening: Hepatitis C antibody (HCV-Ab) positive
- Patients who had a positive test previously or at the Screening for human immunodeficiency virus (HIV) test or who are suspected to be positive for HIV

E 15. Any live attenuated vaccine within 4 weeks prior to the Baseline visit, such as varicella-zoster, oral polio, rubella vaccines (Appendix J). Killed or inactive vaccine may be permitted based on the Investigator's judgment

E 16. Prior or current history of malignancy, including lymphoproliferative diseases, other than adequately-treated carcinoma in-situ of the cervix, nonmetastatic squamous cell, or basal cell carcinoma of the skin, within 5 years prior to the Baseline visit

E 17. Prior or current history of other significant concomitant illness(es) that, according to the Investigator's judgment, would adversely affect the patient's participation in the study. These include, but are not limited to, cardiovascular, renal, neurological disorders (including demyelinating disease), active infectious diseases, endocrinological, gastrointestinal, hepatobiliary, metabolic, pulmonary (eg, severe asthma, cystic fibrosis), nonmalignant lymphoproliferative diseases, other lymphatic disease(s), autoimmune disease, psychiatric disorders, etc.

E 18. Patients with nonhealed/healing skin ulcers

E 19. Surgery within 4 weeks prior to the Screening visit or with planned surgery during the course of the study

E 20. History of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug and known hypersensitivity to any constituent of the product

E 21. History of inflammatory bowel disease, severe diverticulitis, or previous gastrointestinal perforation whatever the cause

E 22. Uncontrolled diabetes mellitus, defined as glycosylated hemoglobin (HbA1c) ≥9% at the Screening visit

E 23. Conditions/situations such as

- Patients with short life expectancy
- Conditions/concomitant diseases making patients non-evaluable for the efficacy endpoints, eg, patients with chronic pain caused by conditions other than JIA, eg, fibromyalgia
- Patients whose immediate family members are dependent (employee) of site/Investigator, and individuals who are institutionalized due to regulatory or legal order.

7.2.2 Exclusion criteria related to the current knowledge of Sanofi compound

E 24. Any of the following laboratory abnormalities at the Screening visit (identified by the central laboratory):

E 25. Female adolescent patients of childbearing potential, unwilling to use, if adequate for age, an effective method of contraception (eg, birth control pills, double-barrier contraception, etc) during treatment and for up to at least 3 months following the last dose (as defined in the informed consent form (ICF) and/or in a local protocol addendum/amendment), and/or who are unwilling or unable to be tested for pregnancy;

Notes: Abstinence may be a possible option depending on local rules and/or regulations; however, if a female patient is abstinent but becomes sexually active during the course of the study, she must be willing to use an effective method of contraception. Sexual counseling will be provided for adolescent patients.

[redacted]

E 26. Positive pregnancy test at Screening or Baseline

E 27. Breast-feeding female adolescent patients.

7.2.3 Additional exclusion criteria during or at the end of Screening

E 28. Patient/parent/legal guardians who has withdrawn consent before enrollment

[redacted]

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Investigational Medicinal Product

Sarilumab, anti-IL-6R mAb (anti-interleukin 6 receptor alpha subunit monoclonal antibody).

Formulation

Sarilumab drug product will be provided at 175 mg/mL in an aqueous buffered vehicle, pH 6.0. It will be supplied in a 5 mL vial filled by 2.7 mL of sarilumab with an extractable volume of 2.0 mL.

Route(s) of administration:

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

For patients receiving Dose Regimens 1 or 2 (q2w), injections will be performed by a professional caregiver at the site during the 12-week core treatment phase of the study. For patients receiving Dose Regimen 3 (weekly injections), arrangements must be made for qualified site personnel or home nurse to administer IMP for the doses that are not scheduled to be given at the study site. For the extension phase of the study, if the patients or the parent(s) or the legal guardian(s) or the caregiver(s) are willing and able to perform the injections, the home injection will be permitted. In those cases, the training will be required and provided to prepare and administer IMP starting at Visit 10 (Week 8) at the core treatment phase. This training must be documented in the patients' study file. The patients or the parent(s) or the legal guardian(s) or the caregiver(s) are allowed to administer the injections **under observation/supervision** by the Investigator(s) or the delegate(s) at Visit 10 (Week 8), Visit 11 (Week 10), and Visit 12 (Week 12) before the allowance for home injection at the extension treatment phase.

On days when the patient has a study visit, the IMP will be administered following clinical procedures and blood collection. Diaries will be provided to record information pertaining to these injections; these diaries will be kept as source data in the patients' study file. If the caregiver is unable or unwilling to administer IMP, arrangements must be made for qualified site personnel to administer IMP for the doses that are not scheduled to be given at the study site.

Dose regimen

Sarilumab should be administered q2w or qw. However, the sarilumab administration window of ±3 days for Dose Regimen 1 and 2 Cohorts, and ±1 day for Dose Regimen 3 Cohort is permitted per protocol to accommodate exceptional circumstances, eg, laboratory test result pending,

ongoing adverse event (AE), patient scheduling difficulty except the Visit 5 (Day 8). There is no administration window at Visit 5 (Day 8). There will be only ±1 day of administration window for patients enrolled in all dose cohorts at Visit 7 (Week 2) and ±1 day of administration window for Dose Regimen 3 Cohort or ±2 for Dose Regimen 1 and 2 Cohorts at Visit 8 (Week 4).

Note that an overdose (accidental or intentional) with the IMP is defined as at least twice the dose during an interval of less than 11 days for q2w administrations and less than 6 days for weekly administration (see Section 10.4.4.1).

The following sarilumab dose is to be administered q2w or qw:

Dose Regimen 1:

- Group A (≥30 kg and ≤60 kg): 2 mg/kg q2w
- Group B (<30 kg and ≥10 kg): 2.5 mg/kg q2w.

Dose Regimen 2:

- Group A (≥30 kg and ≤60 kg): 3 mg/kg q2w
- Group B (<30 kg and ≥10 kg): 4 mg/kg q2w.

Dose Regimen 3:

- Group A (≥30 kg and ≤60 kg): 2 mg/kg qw
- Group B (<30 kg and ≥10 kg): 2.5 mg/kg qw.

Dose modification

The dose (mg) to be administered to patients will be calculated at Baseline. The dose and corresponding volume of drug product will remain the same throughout the course of the 12-week core treatment phase of the trial regardless of change in patient's body weight. In the extension phase, the patient's weight will be measured at each visit and the dose will be adapted to the increase of weight only if the calculation shows a need for dose increase. The dose will be capped at 150 mg and 200 mg for Dose Regimen 1 and 3 and Dose Regimen 2, respectively. Volumes to be injected depending on patient's weight are further detailed in Appendix B.

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCT(S)

Not applicable.

8.3 BLINDING PROCEDURES

Not applicable.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The list of randomized treatment kit numbers will be generated centrally by Sanofi. The IMPs are packaged in accordance with this list. Patients will be assigned a treatment kit by an interactive voice response system (IVRS) or an interactive web response system (IWRS).

Patients who meet the entry criteria will be included and will be dispensed the treatment kits within 2 weight groups (Group A: ≥30 kg and ≤60 kg for patients enrolled during the dose-finding portion and ≥30 kg for patients enrolled during the second and the third portions; Group B: <30 kg and ≥10 kg for all 3 portions).

- For the dose-finding and second portions, the planned ratio of enrollments for the 2 weight groups is 1:1.
- For the third portion, there is no pre-specified enrollment ratio for the 2 weight groups, but each weight group will be capped at 70% (ie, 20 patients). As a result, the most unbalanced enrollments by weight group possible would be 20 versus 8 patients in the third portion.

Patients who meet exclusion criteria may be rescreened once during the open screening period of the study. A different patient identification will be issued. There is no requirement for a waiting period between the screen failure and the rescreening. The IVRS/IWRS report will flag rescreened patients. Patients that are rescreened will be required to sign a new consent form (if the patient has reached the legal age) or by parents or legal guardians. Visit 1 procedures must be repeated (except chest X-ray).

At the Screening Visit 1 (Day-28 to D-1, up to 31 days), the site staff will contact the IVRS/IWRS to obtain a patient number for each patient who gives informed consent. Each patient will be allocated a patient number associated with the center and allocated in chronological order in each site.

At the Baseline Visit 2 (Week 0, Day 1), after confirming the patient is eligible for entry into the treatment period, the site staff will contact the IVRS/IWRS in order to receive the first treatment allocation kit number. To minimize the amount of blood withdrawn and the number of visits while maintaining the evaluation of the primary endpoint, for Group B (<30 kg and ≥10 kg, lighter weight group), patients will be randomly assigned to sarilumab PK sampling schedule 1 or 2 (only applicable for patients in the the dose-finding and second portions) (see Section 9.1.1 for the detailed sarilumab PK sampling schedule). At subsequent visits during the treatment period, the site staff will call IVRS to obtain the next treatment kit number. A confirmation fax/e-mail will be sent to the site after each assignment.

An included patient is defined as a patient who is registered and assigned a treatment kit number. The IMP will also be recorded and tracked on the center IMP inventory forms.

Details of the IVRS/IWRS procedures will be provided to sites in the IVRS/IWRS site manual.

8.5 PACKAGING AND LABELING

The IMP will be provided in patient treatment kits containing labeled vials. The content of the labeling is in accordance with the local regulatory specifications and requirements. One kit contains one vial. The patients will be provided sufficient kits until the next site visit. Additional treatment kits, to provide medication to patients under circumstances, such as a damaged kit, will be allocated by IVRS when a “replacement treatment call” is made to IVRS.

8.6 STORAGE CONDITIONS AND SHELF LIFE

The study medication should be kept refrigerated between 2ºC and 8ºC at the site or at home.

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures and providing proper storage instructions to patients.

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

The IMP may be supplied from the site to the patient via a sponsor-approved courier company where allowed by local regulations and approved by the patient.

8.7 RESPONSIBILITIES

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

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

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) 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 Treatment accountability and compliance

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

- Proper recording of treatment kit number or packaging number as required on appropriate electronic case report form (e-CRF) page for accounting purposes
- All medication treatment kits (whether empty or unused) are returned by the patient at each visit when a treatment dispensing is planned
- The completed home injection diary (returned to the site at each visit), returned treatment kit boxes and any unused and used vials will be used for drug accountability purposes
- The study coordinator tracks treatment accountability/compliance by diary and by counting the number of used treatment kits and fills in the appropriate page of the patient treatment log
- The monitor in charge of the study then checks the data entered on the IMP administration page by comparing them with the IMP that has been retrieved and the patient treatment log form.

8.7.2 Return and/or destruction of treatments

All partially used or unused treatment kits will be retrieved by the Sponsor or destroyed at study site. A detailed treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy the unused IMP, used or partially used kits unless the Sponsor provides written authorization.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s). All medication taken during the study should be recorded on the corresponding pages of the patient e-CRF.

8.8.1 Prohibited medications

The use of any biologic DMARDs, including but not limited to etanercept, adalimumab, infliximab, anakinra, canakinumab, rilonacept, abatacept, rituximab, tocilizumab, and any biologic DMARDs that may become approved during the study is not authorized throughout the study treatment and until 6 weeks following the EOT visit. If any of these treatments are used, the patient should be discontinued from the study treatment and will be asked to perform the scheduled visits and assessments up to EOS visit. (See exclusion criterion E 09 in Section 7.2 for biologic DMARDs off-treatment period).

Treatment with new non-biologic DMARDs should not be initiated during the study. Existing non-biologic DMARDs, such as MTX should be kept at a stable dose unless the patient develops an AE.

Administration of any live (attenuated) vaccine (Appendix J) is contraindicated until 4 weeks following the last dose of IMP administration

Treatment with anti-IL-6 or IL-6R antagonist therapies, including but not limited to tocilizumab or sarilumab (E 08).

Treatment with a JAK inhibitor (such as tofacitinib) (E 10).

8.8.2 Corticosteroids

8.8.2.1 Systemic parenteral and intra-articular corticosteroids

Patients should not receive systemic parenteral glucocorticoids and/or intra-articular glucocorticoid injections (within 4 weeks prior to Baseline), and should not be initiated on new corticosteroids (either systemic or intra-articular) for JIA-related complaints during the 12-week core treatment phase of the study. In the extension period, intra-articular glucocorticoid injections are permitted as clinically indicated for JIA disease flares, if Investigator considers potential benefit outweighs risk of such injection.

8.8.2.2 Oral corticosteroids

Oral steroids may be increased at any time for flare. Oral corticosteroids are permitted if not exceeding 0.5 mg/kg/day (or 30 mg/day) oral prednisone or equivalent at stable dose for at least 2 weeks prior to the Baseline visit.

No change is permitted during the 12-week core treatment phase unless the patient develops an AE (excluding worsening JIA). The dose may be tapered during the extension phase as per the Investigator's recommendations.

If the patient develops an AE for a condition not related to pcJIA that requires a corticosteroid dose modification (eg, increase, or decrease of current concomitant oral prednisone or equivalent), or the introduction of a new oral steroid medication, the dosage modification and AE must be recorded on the patient e-CRF. Furthermore, if this AE occurs during the 12-week core treatment phase, the Sponsor must be notified at the time of the steroid dose modification (eg, within one working day) to verify that the patient can continue to participate in the study.

Glucocorticoid tapering is allowed during the extension phase as per the Investigator's judgment.

8.8.2.3 Intranasal - inhaled or topical corticosteroids

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

8.8.3 Nonsteroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAID) and COX-2 are permitted if taken at a stable dose for at least 2 weeks prior to Baseline. The dose used should be in accordance with the approved dose in the country in which the study is conducted. No change is permitted during the 12-week core treatment phase, unless the patient develops an AE (generally requiring a lowering or discontinuation of NSAID/COX-2 treatment). Patients should not be initiated on new NSAIDs/COX-2 during their participation in the 12-week core treatment phase.

8.8.4 Acetaminophen (paracetamol) and other analgesics

Acetaminophen (paracetamol):

Normal release acetaminophen (not extended release) may be used for pain as required. Acetaminophen use should be limited to ≤80 mg/kg every 24 hours. Specific attention should be paid to co-administration of hepatotoxic drugs.

Other analgesics:

Narcotic or non-narcotic analgesics (with no anti-inflammatory properties) for JIA pain relief are permitted based on Investigator judgment that there is insufficient JIA 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.

8.8.5 Lipid lowering drugs

Lipid lowering drugs are permitted. Dose should be stable for at least 6 weeks prior to Screening. Anti-IL-6 drugs, including sarilumab are known to increase serum cholesterol levels and this effect will be closely monitored during the study. If, during the study, patients are found to have significant increase in cholesterol levels, then the dose of concomitant lipid lowering drug(s) should be adjusted as per local guidelines. A referral to a specialist should be considered when dyslipidemia is difficult to manage.

8.8.6 Cytochrome P450 enzyme substrates

In vitro studies demonstrate that IL-6 reduces cytochrome (CYP)1A2, CYP2C9, CYP2C19, and CYP3A4 enzyme expression; Sarilumab or tocilizumab, which antagonize IL-6, may normalize the formation of CYP450 enzymes. As a result, the therapeutic effect of drugs that are metabolized by these CYP450 isoforms may decrease when RA patients start receiving sarilumab. CYP450 substrates with a narrow therapeutic index should be monitored in patients that enter the open-label core treatment phase and the extension study. Some examples of CYP450 substrates with a narrow therapeutic index that require therapeutic monitoring (PD and/or drug concentration) include: warfarin, cyclosporine, theophylline, digoxin, antiepileptics like carbamazepine (Carbatrol®, Tegretol®), divalproex (Depakote®), phenytoin (Dilantin®), or

valproic acid (Depakene®); or antiarrhythmics, like disopyramide (Norpace®), procainamide (Procan®, Pronestyl®), or quinidine (Quinidex®, Quin-Release Quin-G®).

8.8.7 Other concomitant treatment

8.8.7.1 Topical anesthesia

Topically applied anesthetic creams or pad are permitted based on local guidelines for blood withdrawals and will be used for sarilumab injections only if necessary or based on local guideline.

For Germany only: pain prevention is permitted for all patients and is mandatory for patients aged 6 to 11 years old.

8.8.7.2 Folic/folinic acid

Patients receiving MTX during the study must receive at least the minimum recommended dose of folic acid or folinic acid weekly as per local standard of care.

8.8.7.3 Immunoglobulins

Administration of IV Ig is not permitted during the study or within 15 weeks prior to Baseline. For active varicella infection (chickenpox) or significant exposure to varicella-zoster infection in a patient without history of chickenpox (varicella IgG titer available from Screening), varicella-zoster Igs can be given at the discretion of the Investigator.

8.8.7.4 Growth hormone/androgens

Growth hormone/androgens are not permitted within 4 weeks prior to the Baseline visit, or during the entire study.

8.8.7.5 Iron

Iron may be administered to the patients determined to be anemic at Screening based on the opinion of the Investigator that the anemia is likely due to anemia of chronic inflammation or iron deficiency and iron is likely to be beneficial and there is no contraindication to its use.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PHARMACOKINETICS PRIMARY ENDPOINT

The primary endpoint is: sarilumab PK exposure (maximum serum concentration observed [C_{max}] and area under the serum concentration versus time curve using the trapezoidal method during a dose interval [$AUC_{0-\tau}$]), following the first dose, concentration observed before treatment administration during repeated dosing (C_{trough}) from baseline to Week 12.

9.1.1 Sampling time

For Group A patients (≥30 kg), blood for sarilumab PK sampling will be collected at Visit 2* (Day 1, prior to IMP administration), Visit 3 (Day 3), Visit 4 (Day 5), Visit 5 (Day 8), Visit 6 (Day 12), Visit 7 (Week 2)*, Visit 8 (Week 4)*, Visit 10 (Week 8)*, and Visit 12 (Week 12)*.

For Group B patients (<30 kg and ≥10 kg) enrolled in the dose-finding and second portions, in order to minimize the amount of blood withdrawn, patients will be randomly assigned to sarilumab PK sampling schedule 1 or 2 with the following time points:

- Schedule 1: Visit 2* (Day 1), Visit 3 (Day 3), Visit 5 (Day 8)**, Visit 7 (Week 2)*, Visit 8 (Week 4)*, Visit 10 (Week 8)*, Visit 12 (Week 12)*
- Schedule 2: Visit 2* (Day 1), Visit 4 (Day 5), Visit 6 (Day 12), Visit 7 (Week 2)*, Visit 8 (Week 4)*, Visit 10 (Week 8)*, Visit 12 (Week 12)*.

The sampling schedule for blood collection in 12-week core treatment phase and the extension phases can be found in the study flow charts (see Section 1.2.1 and Section 1.2.2, respectively). For patients for whom the dose will be adjusted to the selected dose regimen, additional PK sampling will be collected for 12 weeks. The sampling schedule for blood collection in these patients can be found in the study flow chart in Section 1.2.2.2.

For patients enrolled in the third portion, the PK sampling visits, ie, Visits 3, 4, 5, and 6 are not applicable during the core treatment phase. The sampling schedule for blood collection in these patients during the extension phase can be found in the study flow chart in Section 1.2.2.3.

If an SAE occurs in a patient, blood samples should be collected for determination of sarilumab concentration and ADA formation at or near the onset and completion of the occurrence of the event, if possible. For patients who discontinue the study treatment prematurely during the core treatment phase (at or before Visit 12) in the dose-finding and second portions, an additional sarilumab PK assessment will be received 2 weeks after the planned EOT assessment (3 weeks after the last IMP injection for Dose Regimen 3 Cohort patients or 4 weeks after the last IMP injection [for Dose Regimen 1 and 2 Cohort patients]). These patients will be asked to return for the EOS assessment 6 weeks after the EOT assessment. The date of the sample collection should be recorded in the patient e-CRF. For early treatment discontinuation patients, blood samples should be collected at the EOS Visit if possible (see flow chart Section 1.2).

Notes:

The nominal sampling times for blood collection on Visit 3 (Day 3), Visit 4 (Day 5) and Visit 5 (Day 8) represent 48, 96, and 168 hours post-dose, respectively.

* On dosing days, PK samples should be collected prior to IMP administration *for all 3 dose regimen cohorts*

**On dosing days, PK samples should be collected prior to IMP administration *for Dose Regimen 3 Cohort.*

9.1.2 Pharmacokinetics handling procedure

It is extremely important to collect all blood samples as close to the protocol specified days as possible (see Section 9.1.1 and study flow chart Section 1.2 for sampling schedule). The reasons for any missed or lost blood samples should be documented. Special procedures for collection, storage and shipping of serum are described in separate operational manuals.

Table 3 - Sample handling procedure for sarilumab and anti-sarilumab antibody

Sample type	Functional Sarilumab	Anti-sarilumab antibody
Matrix	Serum	Serum
Blood sample volume	0.5 ml	0.5 mL[a]
Anticoagulant	None	None
Blood handling procedures	See operation manual	See operation manual
Storage conditions	9 months at -20ºC or below 80ºC (preferred)	24 months at -20ºC or below 80ºC (preferred)
erum hipment Conditions	In dry ice	In dry ice

a For a study visit with blood collection for both pharmacokinetics and anti-sarilumab antibody samples (eg, Baseline Visit 2), it is recommended to draw 1 mL of blood. The serum will be split equally into 2 aliquots to obtain one PK serum aliquot and one anti-sarilumab antibody serum aliquot.

9.1.3 Bioanalytical method

The serum levels of functional sarilumab and anti-sarilumab antibodies will be determined using validated bioanalytical methods.

Table 4 - Summary of bioanalytical method for sarilumab and anti-sarilumab antibody

Bioanalysis	Functional sarilumab	Anti-sarilumab antibody
Matrix	Serum	Serum
Analytical technique	ELISA	Electrochemiluminescence
Assay volume	Variable	Variable
Site of bioanalysis	Regeneron	Regeneron

Abbreviation: ELISA = enzyme-linked immunosorbent assay

9.1.4 Pharmacokinetics parameters

A population PK model will be developed using [redacted] to describe the PK profile of sarilumab. The following pharmacokinetic parameters will be calculated, using the PopPK model for functional Sarilumab in serum. The PK parameters will include, but may not be limited to the following listed in Table 5.

Table 5 - List of pharmacokinetic parameters and definitions

C_{max}	Maximum serum concentration observed
C_{trough}	Concentration observed before treatment administration during repeated dosing
t_{max}	Time to reach C_{max}
AUC_{0-t}	Area under the serum concentration versus time curve calculated using the trapezoidal method during a dose interval (τ)

9.2 SECONDARY ENDPOINT(S)

9.2.1 12-week core treatment phase

The following parameters will be analyzed in 12-week open-label core treatment phase:

- Safety
  - Adverse events (AEs), vital signs, physical examination, laboratory values
  - Acceptability assessments (local tolerability) (see Section 9.3.3)
- Efficacy
  - Juvenile Idiopathic Arthritis ACR30/50/70/90/100 response rate at Week 12
  - Change from baseline in individual JIA ACR components at Week 12
  - Juvenile Arthritis Disease Activity Score (JADAS)-27 change from baseline at Week 12 (see Section 9.4.2)
- Pharmacodynamics
  - Changes in IL-6 associated biomarkers (eg, serum levels of high sensitivity C-reactive protein [hs-CRP], IL-6, total sIL-6R).

9.2.2 Extension part

- Safety
  - Adverse events, vital signs, physical examination, laboratory values
  - Acceptability assessments (local tolerability) (see Section 9.3.3)
- Efficacy
  - Juvenile Idiopathic Arthritis ACR 30/50/70/90/100 response rate at Weeks 24, 48, and every 24 weeks up to the EOS
  - Change from baseline in JIA ACR components at Weeks 24, 48, and every 24 weeks up to the EOS
  - Juvenile Arthritis Disease Activity Score-27 change from baseline at Weeks 24, 48, and every 24 weeks up to the EOS.

9.3 SAFETY ENDPOINTS

9.3.1 Adverse events

Adverse events (AEs), SAEs, adverse events of special interest (AESI), AE that lead to IMP discontinuation and death will be collected from the time of informed consent signature and then at each visit until the EOS. The study specific and general safety criteria are detailed in Section 10.4. To assure the continuing safety of patients in this study, an Independent Data Monitoring Committee will be responsible for reviewing the safety data on a periodic basis throughout the course of the study as outlined in Section 6.2.

Safety Observations

- The Investigator should take all appropriate measures to ensure the safety of the patients. Notably, he/she should follow up the outcome of SAEs/AESI until clinical recovery is complete and laboratory results have returned to normal or until progression has been stabilized or death. In all cases, this may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the Sponsor
- For patients who discontinue the study treatment during the 12-week core treatment phase, these patients will be assessed using the procedure planned for the EOT visit for Visit 27 (Week 156) followed by an additional sarilumab PK assessment 2 weeks after the EOT assessment (the additional PK assessment is only applicable for patients enrolled in the dose-finding and second portions). These patients will be asked to return for the EOS assessment 6 weeks after the EOT assessment. These patients will be asked to perform the protocol scheduled visits and assessments except sarilumab administration until Visit 12.
- For patients who discontinue the study treatment during the extension treatment phase, these patients will be assessed using the procedure planned for the EOT at Visit 27 (Week 156 for dose-finding and second portions/Week 96 for third portion). These patients will be asked to return for the EOS assessment 6 weeks after the EOT assessment.

In case of any SAE/AESI brought to the attention of the Investigator at any time after the EOS for the patient, and considered by him/her to be caused by the investigational product with a reasonable possibility, this should be reported to the Sponsor (see Section 10.4.1.2 and Section 10.4.1.3 for details).

9.3.2 Vital signs

Vital signs include temperature, blood pressure (BP), and heart rate (HR). Please refer Section 1.2.1 and Section 1.2.2 for vital sign time points for patients in the 12-week core treatment phase and extension phase, respectively.

Body temperature

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

Blood pressure

Blood pressure will be measured at each scheduled assessment visit using the same well-calibrated apparatus. Both systolic and diastolic BP should be recorded after the patient has been in a relaxed, semi-supine or supine position for at least 2 minutes. The same arm (the right arm is recommended) should be used to measure BP throughout the study. At each visit requiring BP measurement, two measurements should be taken at the same position at least 1 minute apart (17).

9.3.3 Acceptability assessments (local tolerability)

The patient acceptability (local tolerability) will be evaluated after each IMP injection either at the site or at home. The patients should be monitored at least 30 minutes. The following parameters will be evaluated: presence or absence of bruising, erythema swelling, warmth, burning, stinging, itching, hive formation, pain, induration, mass, discoloration, inflammation and other. In case of any local reaction, the event should be followed up until it resolved. Please refer Section 10.4.2 and Section 10.4.3 for AE or SAE (if applicable) reporting.

For Germany only: After the first IMP administration the patient has to be monitored for at least 1 hour to assess local tolerability.

9.3.4 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.

Blood will be taken at the study site or at home by qualified personnel. If the blood sample is taken on a day of IMP administration, then blood will be sampled before administration of the IMP. Both central and local laboratories will be used for sample assessments and analysis.

Blood sampling limits, as determined by regulatory guidelines, should be followed with these and any other blood testing during the study. To avoid exceeding blood sample limits, a suggested prioritization of tests is provided to Investigators for reference in the laboratory manual.

The following laboratory tests will be performed at designated visits specified in the study flow charts (Section 1.2)

- Hematology including hemoglobin, hematocrit, red blood cell count and morphology (if red blood cell count is abnormal), white blood cell count (WBC) differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) including absolute neutrophil count (ANC) and platelet count will be performed at Visit 1 (Day-28 to Day-1, up to 31 days), the Baseline Visit 2 (Week 0, Day 1), Visit 7 (Week 2), Visit 8 (Week 4), Visit 9 (Week 6), Visit 10 (Week 8), Visit 11 (Week 10), and Visit 12 (Week 12) during the initial core treatment phase and at designated visits during the extension phase (see Section 1.2.2)
- In order to check how the patient's blood cells react on the first dose of study medication, for patients enrolled in the dose-finding and second portions, an additional hematology test must be performed at Visit 6 (Day 12±1 Day) for Dose Regimen 1 and 2 Cohort patients in order to get results before the second dose of sarilumab injection (Visit 7: Week 2, Day 15). For Dose Regimen 3 Cohort patients, an additional hematology test should be performed prior to or at Visit 5 (Day 8) but no earlier than Visit 4 (Day 5) and the results need to be reviewed prior to the second sarilumab injection at Visit 5 (Day 8). The additional hematology test can be done at the central laboratory or at the local laboratory to confirm that the ANC and platelet count are not within the protocol-defined limits for temporary or permanent discontinuation of study drug. For patients enrolled in the third portion without on-site Visit 6, the additional hematology test will be done at the local laboratory before the second dose of sarilumab administration, but no earlier than Day 12. If local laboratory is used, a central laboratory sample for hematology should still be drawn pre-IMP administration at Visit 7 (Day 15, Week 2) as scheduled for Dose Regimen 1 and 2 Cohorts and Visit 5 (Day 8) for Dose Regimen 3 Cohort.
- Complete chemistry profiles will be performed only at the Visit 1 (Day -28 to Day -1, up to 31 days), Baseline Visit 2 (Week 0, Day 1), and Visit 12 (Week 12) during the initial core treatment phase and at designated visits during the extension phase (see Section 1.2.2).
    - Complete chemistry includes: Sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine and creatinine clearance, glomerular filtration rate (using the modified Schwartz formula), calcium, phosphate, total protein, albumin, ALT, AST, alkaline phosphatase (ALP), total bilirubin, conjugated bilirubin, and unconjugated bilirubin

- At Visit 7 (Week 2), Visit 8 (Week 4), Visit 9 (Week 6), Visit 10 (Week 8), and Visit 11 (Week 10) during the initial core treatment phase and at designated visits during the extension phase (see Section 1.2.2) only an abbreviated chemistry profile (ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and albumin) will be measured.

Fasting lipids including total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides will be tested at Visit 1 (Day-28 to Day -1, up to 31 days), Visit 8 (Week 4), Visit 12 (Week 12) during the initial core treatment phase and at designated visits during the extension phase (Section 1.2.2). Patients are required to fast at least 8 hours before the test.

The HbA1c evaluation will only be performed at the Screening based on the patient's medical history and the Investigator's judgment.

- High sensitivity C-reactive protein (hs-CRP) will be evaluated at Visit 1 (Day -28 to Day -1, up to 31 days), the Baseline Visit 2 (Week 0, Day 1), Visit 7 (Week 2), Visit 8 (Week 4), Visit 9 (Week 6), Visit 10 (Week 8), Visit 11 (Week 10), Visit 12 (Week 12) during the initial core treatment phase and at designated visits during the extension phase (see Section 1.2.2).

  Blood samples for ANA/anti double-stranded deoxyribonucleic acid (dsDNA) antibody will be collected at the Baseline Visit 2 (Week 0, Day 1), Visit 12 (Week 12) during the initial core treatment phase and at designated visits during the extension phase (see Section 1.2.2).

  Erythrocyte sedimentation rate (ESR) will be measured at Visit 2 (Week 0, Day 1), and Visit 12 (Week 12) during the initial core treatment phase and at designated visits during the extension phase (see Section 1.2.2).

  Pregnancy test: For females who have commenced menstruating, a serum pregnancy test should be performed at the Screening and the urine pregnancy test should be tested locally at Visit 2 (Week 0, Day 1), Visit 8 (Week 4), Visit 10 (Week 8), and every visit from Visit 12 (Week 12) to Visit 27 EOT (Week 156 for dose-finding and second portions/Week 96 for third portion).

- Optional: Based on patient's family and medical history, the Investigator's judgment, EBV IgG and IgM, hepatitis B and C screening: HBs-Ag, hepatitis B surface antibody (HBs-Ab), total hepatitis B core antibody (HBc-Ab), and hepatitis C antibody (HCV-Ab) may be performed at the Screening Visit 1 (Day -28 to Day -1, up to 31 days). The HIV serology may be performed only based on the Investigator's assessment for those HIV suspected patients. Some tests defined as optional may be required according to local regulations.

  For Argentina and Germany only: Serology testing for hepatitis B and C and HIV have to be performed at Screening visit for all patients in order to screen corresponding exclusion criterion E 14.

- Purified Protein Derivative (PPD) test for patient ≤5 years old or QuantiFERON-TB test for patient >5 years is required to be completed prior to the Baseline Visit 2 (Day 1, Week 0). QuantiFERON-TB test will be considered in the younger group of patients (≤5 years old) based on the local PPD availability, local regulation for PPD screening and the Investigator's judgments.

  Patients with PPD tests should be evaluated within 48 to 72 hours after placement of the PPD skin test (for patients who fail to be evaluated within 72 hours, the skin test should be repeated). An assessment of the level of risk (TB contact and/or recent immigration from a country with a high prevalence of TB) should be taken into consideration when defining the result of the skin tests. Refer to exclusion criteria E 13. The TB test should be performed at Visit 18 (Week 48), Visit 22 (Week 96), and Visit 26 (Week 144, not applicable for the third portion), approximately 1, 2, and 3 years, respectively after the patient is enrolled in the study. Tuberculosis risk assessment will be done at every visit throughout the study.
- Urine analysis including specific gravity, pH, glucose, blood, protein, nitrites, leukocyte esterase and bilirubin, will be performed at the Screening Visit 1 (Day-28 to Day-1, up to 31 days) using a dipstick. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. For any abnormal dipstick result, microscopic analysis will be performed by central laboratory.

9.4 EFFICACY ENDPOINTS

9.4.1 Juvenile idiopathic arthritis American college of rheumatology response

The JIA ACR rating scale to assess signs and symptoms will be used in this study (refer to Section 1.2).

The JIA ACR 30/50/70/90/100 response is defined as a patient with 3 of 6 core set variables improved by at least 30%/50%/70%/90%/100% from baseline with no more than 1 of the remaining variables worsened by more than 30% Appendix C. The JIA ACR core set includes 6 variables:

- Physician global assessment of disease activity
- Patient/parent assessment of overall well-being
- Functional ability determined by Childhood Health Assessment Questionnaire (CHAQ)
- Number of joints with active arthritis (0-71 joints)
- Number of joints with limitation of motion (0-67 joints)
- High sensitivity C-reactive protein.

During the 12-week core treatment phase, JIA ACR disease core set will be evaluated at every site visit except Visit 3 (Day 3), Visit 4 (Day 5), Visit 5 (Day 8), and Visit 6 (Day 12). During the extension phase (for patients who remain on the current dose (selected dose regimen), the JIA ACR core set will be assessed periodically at Weeks 24, 48, 72, 96 (EOT for third portion), 120 (not applicable for third portion), 144 (not applicable for third portion), and EOT (Week 156 for dose-finding and second portions/Week 96 for third portion). For patients who change to the selected dose regimen during the extension phase, please refer to Section 1.2.2.2.

9.4.1.1 Physician global assessment of disease activity

Physician's global assessment of disease activity will be performed at Screening, at Baseline prior to IMP administration and at each designated site visit until the EOT visit. The Investigator will be requested to rate the patient's disease activity on an anchored 100 mm horizontal visual analogue scale (VAS) where 0 is considered the best disease activity and 100 the worst (see Appendix D).

9.4.1.2 Patient/parent assessment of overall well-being

Patient/parent assessment of overall well-being will be measured on a 100 mm horizontal VAS at Screening, at Baseline prior to dosing and at each designated site visit until the EOT visit. The patient or the same parent or the same guardian should be requested to complete the form to ensure the consistency (see Appendix D)

9.4.1.3 Childhood health assessment questionnaire

The CHAQ is an interview or self-administered instrument for children ≥8 and parent/proxy-administered for children younger than 8 years of age. The CHAQ is a generic measure of health status in children ages 1 to 19 years of age. The Spearman's correlation coefficient between Disability Index scores from questionnaires administered to parents and those administered to other children (>8 years) was 0.84 (n = 29; $p<0.001$), demonstrating that parents can accurately report for their children. The face validity of the instrument was evaluated by a group of 20 health professionals and parents of 22 healthy children. The assessment consists of 43 items in total and takes approximately 10 minutes to complete. The CHAQ questionnaire will be completed before IMP dosing and at subsequent time points (as per guidance provided by the health economics and outcomes research department). The recall period is 1 week (18). In this case, the actual date of the CHAQ questionnaire will be recorded in the e-CRF.

The median CHAQ scores corresponding to mild, mild-to-moderate and moderate disability reported in the development of the CHAQ were 0.13, 0.63, and 1.75 respectively (19).

In order to eliminate discrepancies which could be introduced by growth and development, parents are asked to note only those difficulties due to illness (eg, if child unable to do an activity because too young, mark response as "not applicable"). Response options assessing difficulty are based on a 5 point Likert scale (0 = Without Any Difficulty, 1 = with some Difficulty, 2 = With MUCH difficulty, 3 = Unable to do and 4 = Not Applicable).

Part 1 of the CHAQ is the Disability Index which contains 41 items assessing ability to function in daily life. The following 8 subscales/domains: 1. Dressing and Grooming, 2. Arising, 3. Eating, 4. Walking, 5. Hygiene, 6. Reach, 7. Grip, and 8. Activities. For each domain: (a) ratings of the degree to which daily functions are difficult to perform (items 6-9, 12-13, 16-18, 21-22, 34-38, 41-44, 47-51, and 54-58); (b) require use of special aides or devices (item 24-27, 60-62) and (c) require assistance from another person (items 29-30, 64-65) are assessed.

- To calculate the CHAQ-DI each domain score is first calculated:
  - The question with the highest response determines the score for that functional area
  - If aids or devices are used or help is needed to complete tasks in a certain area, a minimum score of 2 is recorded for the corresponding functional area
  - The 8 subscales/domains are averaged to calculate a mean score which is the Disability Index (with range of 0-3).

Lower disability index scores indicate better than health status/better healthier related quality of life/less signs and symptoms while higher disability index scores indicate worse health status/worse HRQL/more signs and symptoms (18, 20).

The minimal clinical important improvement in CHAQ-disability index is a reduction in score of 0.13. The minimal clinical important deterioration in the CHAQ-disability index is a median change score of 0.75 (19).

Part 2 of the CHAQ is the Discomfort Index while Part 3 of the CHAQ is the Health Status measure; both are measured on separate 15-cm scales.

The CHAQ-Discomfort Index is determined by the severity of pain in the past week, rated on a VAS (with anchors of “0 no pain” and “100 very severe pain”).

- To calculate the CHAQ-discomfort index (item 67)
  - Measure the distance from the left end of the VAS in item 67 to the respondent’s mark and multiply by 0.2 Range is 0.3. The Discomfort Index score can be rescaled to a 0-100 scale.

The Part 3 of the CHAQ Health Status score measure the patient’s or parent’s global assessment of illness.

- To calculate the CHAQ Health Status score (item 69)
  - Measure the distance from the left end of the VAS in item 69 to the respondent’s mark and multiply by 0.2 Range is 0-3. The Health Status score can be rescaled to a 0-100 scale, see Appendix E.

9.4.1.4 Number of Joints with active arthritis and number of joints with limited motion

An active joint is defined as joint with

- Swelling within join not due to deformity, OR
- Limitation of motion with either pain or tenderness

Seventy-one joints will be assessed for active disease by counting the number of the joints with swelling not due to deformity OR limitation of motion with either pain or tenderness or both (21, 22).

Cervical spine (counts as 1 joint), Temporomandibular (2 joints, R and L side), Sternoclavicular (2 joints), Acromioclavicular (2 joints), Shoulder (2 joints), Elbow (2 joints), Wrist (2 joints), Metacarpophalangeal (10 joints total, 5 on each side), Proximal interphalangeal (10 joints total, 5 on each side), Distal interphalangeal (8 joints total, 4 on each side), Hip (2 joints), Knee (2 joints), Ankle (2 joints), Subtalar (2 joints), Tarsometatarsal (2 joints), Metatarsophalangeal (10 joints, 5 on each side), and Foot interphalangeal (10 joints, 5 on each side) total 71 joints.

Sixty-seven joints will be examined for limitation of motion are the same as those examined for active disease except the sternoclavicular (n = 2) and acromioclavicular (n = 2). A formal count of the joints will be performed by a trained assessor. Joint tenderness is defined as pain induced by the pressure of the joints, exerted by the assessor's thumb and index finger.

9.4.1.5 High sensitivity C-reactive protein

High sensitivity C-reactive protein (hs-CRP) will be evaluated at Visit 1 (Day-28 to Day -1, up to 31 days), the Baseline Visit 2 (Week 0, Day 1), Visit 7 (Week 2), Visit 8 (Week 4), Visit 9 (Week 6), Visit 10 (Week 8), Visit 11 (Week 10), Visit 12 (Week 12) during the initial core treatment phase and at designated visits during the extension phase (see Section 1.2.2). High sensitivity C-reactive protein levels are directly correlated with IL-6R activity. It is expected that active dose regimens will have a dramatic lowering effect on CRP levels.

9.4.2 Juvenile arthritis disease activity Score

The JADAS includes 4 measures:

- Physician global assessment of disease activity measured on a 10-cm VAS where 0 = no activity and 10 = maximum activity
- Parent/patient global assessment of well-being, measured on a 10-cm VAS where 0 = very well and 10 = very poor
- Count of joints with active disease
- Erythrocyte sedimentation rate (ESR) normalized to a 0-10 scale according to the following formula:
  - [ESR (mm/hour)-20]/10

- Before making the calculation, ESR value <20 mm/hour converted to 0 and ESR values >120 mm/hour were converted to 120.

The JADAS will be calculated as the simple linear sum of the scores of its 4 components. (23).

The JADAS-27 includes the following joints: cervical spine, elbows, wrists, metacarpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees, and ankles. The JADAS was found to be a valid instrument for assessment of disease activity in JIA and is potentially applicable in standard clinical care, observational studies and clinical trials (23). JADAS-27 will be calculated at Visit 12 (Week 12) during the initial core treatment phase and at designated visits during the extension phase (see Section 1.2.2).

9.5 PHYSICAL EXAMINATION

A complete physical examination will be performed at the Screening Visit 1 (Day -28 to Day -1, up to 31 days), Visit 2 (Day 1, Week 0), Visit 8 (Week 4), Visit 9 (Week 6), and Visit 12 (Week 12) during the initial core treatment phase and at designated visits during the extension phase (see Section 1.2.2). Any clinically significant abnormalities should be reported in the patient e-CRF as medical history if observed at Visit 1 (Day -28 to Day -1, up to 31 days) and reported as an AE if observed at Visit 2 (Day 1, Week 0) and during subsequent visits. Any clinically significant physical examination abnormality known at the Screening visit should be reported as medical history and not an AE. Clinically significant abnormalities or worsening from Baseline reported after the Screening visit should be reported as AEs.

9.6 WEIGHT

Weight should be taken with the patient wearing undergarments or very light clothing (without outerwear or accessories) and no shoes and with an empty bladder. Weight is to be determined to nearest 0.1 kg.

The same scale is recommended to be used throughout the study. Weight will be collected at the Screening Visit 1 (Day -28 to Day -1, up to 31 days), Baseline Visit 2 (Day 1, Week 0), Visit 12 (Week 12), and every visit during the extension phase except for some visits for patients who change to the selected dose regimen (no assessment done at Visit 102 (Week 2) and Visit 104 (Week 6) for patients who changed to selected dose regimen).

9.7 PHARMACODYNAMICS

9.7.1 Pharmacodynamics parameters

Pharmacodynamic effects of sarilumab will be assessed through measurement of the following biomarkers: hs-CRP, IL-6, total sIL-6R.

9.7.1.1 Assessment methods

The sample handling procedure for total sIL-6R and IL-6 is summarized in Table 6. Special procedures for collection, storage and shipping of serum are described in separate operational manuals. The sample procedure for hs-CRP is described in Section 9.4.1.5 and Section 9.3.4.

Table 6 - Summary of handling procedures for total sIL-6R and IL-6

Sample type	sIL-6R	IL-6
Blood sample volume	0.5 ml	0.5 mL
Anticoagulant	NONE	None
handling procedures	Refer to Lab Manual	Refer to Lab Manual
Aliquot split	One aliquot	One aliquot
Storage conditions	-70°C (if not available, -20°C)	-70°C (if not available, -20°C)
Shipment Conditions	In dry ice	In dry ice

Abbreviations: IL = interleukin, sIL-6R = soluble interleukin-6 receptor.

9.7.1.2 Assessment schedule

The sampling schedule for blood collection can be found in the study flow chart (see Section 1.2). IL-6 and total sIL-6R will be measured at the Baseline Visit 2 (Week 0) and Visit 12 (Week 12). For patients who discontinue the study treatment prematurely during the core treatment phase, the IL-6 and total sIL-6R will be measured at the EOT assessment.

9.8 IMMUNOGENICITY

Immunogenicity of sarilumab will be assessed through measurement of anti-sarilumab antibodies (ADA). Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. The sampling schedule for blood collection can be found in the study flow charts (see Section 1.2).

9.9 PHARMACOGENOMICS

Parent(s) or legal guardian(s) will be required to sign a separate ICF for (optional) saliva sample collection. The DNA samples for the genomic research will be double-coded as defined by the International Council for Harmonisation (ICH) guideline E15. DNA samples may be stored for up to 15 years after the final date of the clinical study report (CSR) and may be used for research purposes. For saliva sampling collection, please refer to the Laboratory Manual.

The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response to target modulation, disease prognosis and progression, or other clinical outcome measures. These data may be used or combined with data collected from other studies to identify genomic markers that may predict response and elucidate mechanisms of disease. Analyses may include sequence determination or single nucleotide polymorphism studies of

candidate genes and surrounding genomic regions. Genome-wide studies, including (but not limited to) single nucleotide polymorphism analyses, genomic sequencing, and transcriptome sequencing may also be performed. If indicated, genomic analyses may also be performed to identify markers associated with toxicity.

Patients are still eligible to enroll in the study if they and their parents or legal guardians do not wish to participate in the pharmacogenomic sample collection.

9.10 APPROPRIATENESS OF MEASUREMENTS

The pharmacokinetic and pharmacodynamics assessments used in this study are standard for the evaluation of the anti-IL-6. The efficacy and safety assessments used in this study are appropriate for the evaluation of DMARD in patients with pcJIA.

9.11 FUTURE USE OF SAMPLES

Any unused or left-over serum samples collected for drug concentration or ADA measurements may be stored and used for exploratory biomarker research related to pcJIA, inhibition of the IL-6Rα pathway with an antibody, treatment response (PD and or predictive), to investigate unexpected AEs, or to identify markers associated with toxicity. Samples may be stored up to 15 years after the date of the CSR or based on local regulation.

The decision for unused or left-over serum samples retention is entirely voluntary. The patient/the parent(s)/guardian(s) will be required to sign a separate consent form for the future use of samples. If the patients or the parent(s) or the guardian(s) do not wish to keep the unused or left-over serum samples, this will not have an effect on the patient’s participation in the main study and will not affect the quality of his/her care.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

It is preferred that all study visits take place in the morning when fasting blood samples are required. A non fasting condition could overestimate LDL/triglycerides value which will affect notification of related AEs/AESIs. To permit reliable results, fasting status for at least 8 hours is required for each visit at which fasting lipids laboratory tests will be performed. If the test is performed centrally, both the duration of fasting and the reason of no fasting will be reported in central laboratory data base.

For all visits, a time frame of ±1 day for Dose Regimen 3 Cohort and ±3 days for Dose Regimen 1 and 2 Cohorts is acceptable using Day 1 as reference except for:

- Visit 3 (Day 3), Visit 4 (Day 5), and Visit 5 (Day 8), no visit window is allowed where PK sampling occurs
- Visit 6 (Day 12) ±1 day for all applicable dose regimen cohorts
- Visit 7 (Week 2) ±1 day for all dose regimen cohorts
- Visit 8 (Week 4) ±2 days for Dose Regimen1 and 2 Cohorts; and ±1 day for Dose Regimen 3 Cohort.

The previous laboratory testing needs to be reviewed by the Investigator or Investigator's designee based on local guidelines before IMP administration and dispense. The results of the evaluation will be recorded on the appropriate e-CRF pages.

Patients who discontinue the study treatment prematurely will be assessed using the procedure planned for the EOT (Visit 27) These patients will be asked to return for the EOS assessment 6 weeks after the EOT visit (Visit 28/EOT+ 6 weeks). For patients who discontinue the study treatment during the 12-week core treatment phase (at or before Week 12), there will be an additional PK assessment 2 weeks after the EOT visit (Visit 88/EOT + 2 weeks) (the additional PK assessment is only applicable for patients in the dose-finding and second portions). For patients who discontinue the study treatment permanently during the 12-week core treatment phase, these patients should return for the protocol scheduled visits for the planned assessments without study medication administration until Visit 12.

Screening Period (Day -28 to Day -1 + 3 days, maximum up to 31 days)

10.1.1 Visit 1: Screening (Day -28 to Day -1, up to 31 days) for all patients

Prior to all screening assessments, the patient (if he/she has reached the legal age of consent based on local guidelines), the parent(s) or the legal guardian(s) must sign and date the Ethics Committee approved ICF. The patient assent should be obtained depending on his/her maturity of understanding study associated information. All patients, parent(s), and the legal guardian(s) will

receive information on the study objective(s) and procedures from the Investigator. Separated ICFs should be obtained for patients who are going to participate in the optional saliva sample collection for genomic analysis and agree to keep left-over blood samples for future research. A separate (locally approved) ICF will be completed by any patients requiring genetic Gilbert disease testing as per local regulations.

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for them to be performed over more than 1 site visit if necessary, as long as the Screening visit window prior to the Baseline Visit 2 (Day 1) is respected.

Patients who fail screening for exclusion criteria such as concomitant medications, required drug-specific discontinuation periods or laboratory abnormalities, may be rescreened for study eligibility 1 additional time. The site has first to contact IVRS to declare the patient as screen failure and then contact IVRS again to re screen the patient (see Section 8.4).

Laboratory retesting is allowed during the Screening visit without sending a screen failure notice to IVRS for rescreening if the result of the corresponding retest is expected during the screening period in the following conditions:

- Blood sample issues, (eg, sample clot, hemolysis, indeterminate results received from central laboratory)
- Laboratory result does not reflect the patient's condition, or if this retest is medically justified as per Investigator judgment
- At the Investigator's discretion laboratory tests mentioned in exclusion criterion E 24 may be repeated by central laboratory retesting between the Screening visit and the first IMP administration to ensure the patient meet eligibility with respect to exclusion criterion E 24. A locally approved specific consent form will be signed by patients who require Gilbert syndrome genetic testing (consent/assent must be obtained prior to performing this assessment and local regulations should be respected).

The Screening visit will include the following procedures and assessments (see Section 1.2) in the study flow chart. The following items will then be checked and recorded:

- Call IVRS for notification of Screening and assign a patient number
- Interview to collect patient demographic information (including race and ethnicity), previous medical and surgical history. Medical history should include in particular JIA history, in order to confirm (a) the diagnosis; (b) the patient's intolerance or inadequate response to the current treatment and/or non-biologic DMARD
- Assess eligibility by review of inclusion/exclusion criteria. Patients who do not meet these inclusion/exclusion criteria should not continue the Screening process
- Review prior and concomitant medications including biologic and non-biologic DMARDs such as MTX (see Section 8.8.1). Record duration of treatment, dosage, date and reason for discontinuation, the period between the last treatment date with a biologic DMARD and JAK kinase inhibitor treatment (see E 10 and Section 8.8.1)
- Collect the vaccination history

- Record vital signs including body temperature, BP, and HR
- Record weight (kg) and height (cm)
- Check Tanner stage (see Appendix F) and menstruation status for female patients
- Inquire regarding AEs/SAEs
- Perform a tuberculosis risk assessment. In case of suspicion of tuberculosis, refer the patient to a specialist for a complete examination and additional work-up.
- Perform a complete physical examination including skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, lymphatic examinations, complete neurological examinations, and musculoskeletal systems.
  - If abnormal clinically significant already known report medical history
  - If new abnormal clinically significant (discover at Visit 1) report AE
- Perform the joint count assessments to note JIA disease manifestations (articular and extra-articular) and assess disease activity. Any abnormalities should be recorded and documented in prior medical/surgical history
- Collect fasting blood for hematology (see Section 9.3.4), chemistry (including sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatinine clearance, glomerular filtration rate, calcium, phosphate, total protein, albumin, ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated, and bilirubin), fasting lipids, HbA1c (based on the Investigator's judgment), hepatitis B and C, EBV and HIV serology (based on medical history and the Investigator's judgment), hs-CRP, and serum pregnancy test for female patients who have commenced menstruating (see Section 9.3.4 and the study flow chart Section 1.2)

  For Argentina and Germany only: Serology testing for hepatitis B and C and HIV have to be performed at Screening visit for all patients in order to screen corresponding exclusion criteria E 14
- Perform PPD tuberculin skin test for patients ≤ 5 years or QuantiFERON-TB Gold for patients >5 years. PPD or QuantiFERON-TB is required to be completed prior to the Baseline Visit 2 (Day 1, Week 0). Purified Protein Derivative (PPD) results must be evaluated within 48 to 72 hours after placement of the PPD skin test (for patients who fail to be evaluated within 72 hours, the skin test should be repeated). An assessment of the level of risk (TB contact and/or recent immigration from a country with a high prevalence of TB) should be taken into consideration when defining the result of the skin tests. Refer to exclusion criteria E 13 for the details
- Chest X-ray: may be performed for the patients only when deemed necessary based on the Investigator's judgment or in line with local guideline for TB screening prior to initiating a biologic therapy for JIA patients who haven't had chest X-ray performed within 3 months prior to the Baseline Visit 2 (Day 1, Week 0)
- Obtain urine for urinalysis (dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory

- Schedule the appointment for Visit 2 Baseline (Day1, Week 0) for patients who meet all the inclusion criteria and none of the exclusion criteria.

Core Treatment Period (Visit 2 [Day 1, Week 0] ~ Visit 12 [Week 12]; up to 12 Weeks)

10.1.2 Visit 2 Baseline (Day 1, Week 0)

- Reconfirm eligibility by reviewing of inclusion/exclusion criteria with particular attention to exclusion criteria (see Section 7.2) and concomitant medication use (see Section 8.8)
- Call IVRS to inform the Baseline Visit 2 (Day 1, Week 0) and get the treatment kit number(s) assigned to each patient along with the dose volume to be administered. For Group B patients in the dose-finding and second portions, in order to minimize the amount of blood withdrawn, patients will be randomly assigned to sarilumab PK sampling schedule 1 or 2 (see Section 9.1.1)
- Remind parent(s) and legal guardian(s) to sign a separate ICF for optional saliva sample collection for genomic studies and left-over blood samples for future research (see Section 9.9 and Section 9.11)
- Inquire regarding AEs/SAE
- Record concomitant medications use with start date and dose in the patient's e-CRF
- Record vital signs including body temperature, BP, and HR
- Record weight (kg) and height (cm)
- Perform a complete physical examination including skin, nasal cavities, eyes, ears respiratory, cardiovascular, gastrointestinal, lymphatic, neurological systems, and musculoskeletal systems.
- Perform the joint count assessments to note JIA disease manifestations (articular and extra-articular) and assess disease activity. Any abnormalities should be recorded and documented in prior medical/surgical history (ensure JADAS-27 joints are included)
- Complete the physician global assessment of disease activity
- Ask the patient/parent(s)/guardian(s) to complete relevant questionnaires: functional ability determined by CHAQ and (parent or guardian)/patient assessment of overall well-being. All questionnaires should be documented in the subject's study file. Each VAS score should be copied on the patient's e-CRF
- Perform a tuberculosis risk assessment. In case of suspicion of tuberculosis, refer the patient to a specialist for a complete examination and additional work-up.
- Collect blood for hematology (see Section 9.3.4), complete chemistry (including sodium, potassium, chloride, bicarbonate, BUN, creatinine, creatinine clearance, calcium, phosphate, total protein, albumin, ALT, AST, ALP, total bilirubin, conjugated bilirubin, and unconjugated bilirubin; see Section 9.3.4), hs-CRP, ESR, RF, ANA, anti-double stranded DNA (anti-dsDNA)

- Collect blood samples for serum sarilumab and antibodies to sarilumab, IL-6, and total sIL-6R (see Section 9.1 and the study flow chart Section 1.2)
- Collect optional saliva sample (as appropriate). This is optional. The samples are preferably collected at the Baseline Visit 2 (Day 1), however it may be collected at any time during the study
- Perform urine pregnancy test locally for the female patients who have commenced menstruation
- Dispense the IMP to those patients who are at the Dose Regimen 3 Cohort for home injection
- Provide home diary to Dose Regimen3 Cohort patients to record information pertaining to injections performed at home (date, time, injection location, and any problems) at each intermediate on-site visit. The completed diary will be reviewed at the next scheduled visit. In case sarilumab PK sampling is performed at home during the core treatment phase (Visit 3, Visit 4, Visit 5 and Visit 6) a PK diary will be provided to collect real date and time of the samples. This PK diary should be delivered by the site to the nurse/qualified personnel, completed by the nurse/qualified personnel then returned to the site. This PK diary will be reviewed at each visit when applicable
- Administer the IMP
  - Patients should be monitored for at least 30 minutes after IMP administration for any signs or symptoms of a hypersensitivity reaction
  - For Germany only: After the first IMP administration the patient has to be monitored for at least 1 hour to assess local tolerability
- Check local tolerability (see Section 9.3.3)
- Schedule the appointment for Visit 3 (Day 3) for blood sample collection or Visit 4 (Day 5) depending the PK schedule (only applicable for dose-finding and second portions)
- Schedule the appointment for Visit 7 (Week 2), and ask the patient to come in fasting condition and instruct for performing an additional hematology test locally before Visit 7, but no earlier than Day 12 in order to get results prior to the second dose of sarilumab administration to confirm that the ANC and platelet counts are not within the protocol-defined limits for temporary or permanent discontinuation of study drug (only applicable for third portion)

10.1.3 Visit 3 (Day 3), Visit 4 (Day 5), Visit 5 (Day 8), and Visit 6 (Day 12)

For patients enrolled in the third portion, Visits 3, 4, 5, and 6 are not applicable.

Visit 3 (Day 3), Visit 4 (Day 5), Visit 5 (Day 8), and Visit 6 (Day 12) are serum PK sample collection visits (see flow chart Section 1.2) with no visit window permitted for Visit 3 (Day 3), Visit 4 (Day 5), and Visit 5 (Day 8). There is ±1 day window allowed for Visit 6 (Day 12). In case the patient is unable to have the blood collection at the site, a home nurse should be arranged to collect the blood at home and the IMP should be brought for patients who are at Dose Regimen 3

Cohort for injection at Visit 5 (Day 8). All the blood collection, storage, and shipment conditions should be strictly followed. Concomitant medications and AEs/SAEs will be inquired at these visits.

- For Group A, sample collection at Visit 3 (Day 3), Visit 4 (Day 5), Visit 5 (Day 8), and Visit 6 (Day 12) for patients in Dose Regimen 1, 2, and 3 Cohorts
- For Group B, in order to minimize the amount of blood withdrawn, patients will be randomly assigned to sarilumab PK sampling schedule 1 or 2 with the following time points (see Section 9.1.1):
  - Schedule 1: Visit 3 (Day 3), Visit 5 (Day 8)
  - Schedule 2: Visit 4 (Day 5), Visit 6 (Day 12).

Visit 3 (Day 3)

- Record all concomitant medications use with start date and dose in the patient's e-CRF
- Sarilumab PK sampling will be performed for Group A patients and for Group B patients who are in Schedule 1.

Visit 4 (Day 5):

- Record all concomitant medications use with start date and dose in the patient's e-CRF
- Sarilumab PK sampling will be performed for Group A patients and for Group B patients who are in Scheduled 2
- An additional hematology test will be performed for Dose Regimen 3 Cohort patients prior to or at Visit 5 (Day 8) but no earlier than Visit 4 (Day 5) and the results need to be reviewed prior to the second sarilumab injection at Visit 5 (Day 8) to confirm that the ANC and platelet count are not within the protocol-defined limits for temporary or permanent discontinuation of study drug.

Visit 5 (Day 8):

- Record all concomitant medications use with start date and dose in the patient's e-CRF
- The Visit 2 (Day 1) hematology laboratory assessment and the additional hematology test results must be reviewed before the administration of the second dose of sarilumab injection at Visit 5 (Day 8) for Dose Regimen 3 Cohort patients
- Sarilumab PK sampling will be performed for Group A patients and for Group B patients who are in Schedule 1
- For the Dose Regimen 3 Cohort patient who used local laboratory for the additional hematology test, a central laboratory sample for hematology should still be drawn pre-IMP administration and preferred at Visit 5 (Day 8)
- Investigational medicinal product administration and local tolerability check for Dose Regimen 3 Cohort patients at Visit 5 (Day 8)

Visit 6 (Day 12)

- Record all concomitant medications use with start date and dose in the patient's e-CRF
- Sarilumab PK sampling will be performed for Group A patients and for Group B patients who are in Schedule 2
- An additional hematology test must be performed at Visit 6 (Day 12 ±1 Day) for patients in the Dose Regimen 1 and 2 Cohorts in order to get results before the second dose of sarilumab administration (Visit 7; Week 2, Day 15) to confirm that the ANC and platelet count are not within the protocol-defined limits for temporary or permanent discontinuation of study drug.

10.1.4 Visit 7 (Week 2)

The Visit 2 (Day 1) hematology laboratory assessment and the test results for additional hematology test performed prior to the second sarilumab administration for Dose Regimen 1 and 2 Cohort patients must be reviewed before the second dose of sarilumab injection scheduled at Visit 7 (Day 15, Week 2) to confirm that the ANC and platelet count are not within the protocol-defined limits for temporary or permanent discontinuation of study drug. If a local laboratory was used for the additional hematology test at Visit 6 (Day 12 ±1 Day), a central laboratory sample for hematology should be drawn pre-IMP administration at this visit as scheduled for Dose Regimen 1 and 2 Cohorts.

- Record all concomitant medications use with start date and dose in the patient's e-CRF
- Inquire regarding AEs/SAEs
- Check home diary/compliance for Dose Regimen 3 Cohort patients
- Provide home diary to Dose Regimen 3 Cohort patients to record information pertaining to injections performed at home (date, time, injection location, and any problems) at each intermediate on-site visit. The completed diary will be reviewed at the next scheduled visit
- Perform the joint count assessments to note JIA disease manifestations (articular and extra-articular) and assess disease activity
- Complete the physician global assessment of disease activity
- Ask the patient/parent(s)/guardian(s) to complete relevant questionnaires: functional ability determined by CHAQ and (parent or guardian)/patient assessment of overall well-being. All questionnaires should be documented in the subject's study file. Each VAS score should be copied on the patient's e-CRF
- Perform a tuberculosis risk assessment. In case of suspicion of tuberculosis, refer the patient to a specialist for a complete examination and additional work-up
- Collect blood for hematology (see Section 9.3.4), chemistry including ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and albumin
- Collect blood samples for hs-CRP and serum sarilumab (see Section 9.1 and the study flow chart Section 1.2)

- Call IVRS to register the visit and get the treatment kit number(s) assigned to each patient along with the dose volume to be administered
- Dispense the IMP to those patients who are at the Dose Regimen 3 Cohort for home injection
- Administer the IMP
  - Patients should be monitored for at least 30 minutes after each IMP administration for any signs or symptoms of a hypersensitivity reaction
- Check local tolerability (see Section 9.3.3)
- Schedule the appointment for Visit 8 (Day 29, Week 4) and request the patient to come in fasting condition.

10.1.5 Visit 8 (Week 4)

- Record all concomitant medications use with start date and dose in the patient's e-CRF
- Inquire regarding AEs/SAEs
- Check home diary/compliance for Dose Regimen 3 Cohort patients
- Record vital signs including body temperature, BP and HR
- Perform a complete physical examination including skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, lymphatic examinations, complete neurological examinations, and musculoskeletal systems.
- Perform the joint count assessments to note JIA disease manifestations (articular and extra-articular) and assess disease activity.
- Provide home diary to Dose Regimen 3 Cohort patients to record information pertaining to injections performed at home (date, time, injection location, and any problems) at each intermediate on-site visit. The completed diary will be reviewed at the next scheduled visit
- Ask the patient/parent(s)/guardian(s) to complete relevant questionnaires: functional ability determined by CHAQ and (parent or guardian)/patient assessment of overall well-being. All questionnaires should be documented in the subject's study file. Each VAS score should be copied on the patient's e-CRF
- Complete the physician global assessment of disease activity
- Perform a tuberculosis risk assessment. In case of suspicion of tuberculosis, refer the patient to a specialist for a complete examination and additional work-up
- Collect blood for hematology (see Section 9.3.4), chemistry including ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and albumin, fasting lipid, and hs-CRP
- Collect blood samples for serum sarilumab (see Section 9.1 and the study flow chart Section 1.2)

- Perform urine pregnancy test locally for female patients who have commenced menstruating
- Call IVRS to register the visit and get the treatment kit number(s) assigned to each patient along with the dose volume to be administered
- Dispense the IMP to those patients who are at the Dose Regimen 3 Cohort for home injection
- Administer the IMP
  - Patients should be monitored for at least 30 minutes after IMP administration for any signs or symptoms of a hypersensitivity reaction.
- Check local tolerability (see Section 9.3.3)
- Schedule the appointment for Visit 9 (Week 6).

10.1.6 Visit 9 (Week 6), Visit 10 (Week 8), Visit 11 (Week 10)

- Record all concomitant medications use with start date and dose in the patient's e-CRF
- Inquire regarding AEs/SAEs
- Check home diary/IMP compliance
- Provide home diary to Dose Regimen 3 Cohort patients to record information pertaining to injections performed at home (date, time, injection location, and any problems) at each intermediate on-site visit. The completed diary will be reviewed at the next scheduled visit
- Record vital signs including body temperature, BP and HR at Visit 10 (Week 8)
- Perform a complete physical examination including skin, nasal cavities, eyes, ears respiratory, cardiovascular, gastrointestinal, lymphatic, neurological systems, and musculoskeletal systems at Visit 9 (Week 6)
- Perform the joint count assessments to note JIA disease manifestations (articular and extra-articular) and assess disease activity
- Ask the patient/parent(s)/guardian(s) to complete relevant questionnaires: functional ability determined by CHAQ and (parent or guardian)/patient assessment of overall well-being. All questionnaires should be documented in the subject's study file. Each VAS score should be copied on the patient's e-CRF
- Complete the physician global assessment of disease activity
- Perform a tuberculosis risk assessment. In case of suspicion of tuberculosis, refer the patient to a specialist for a complete examination and additional work-up
- Collect blood for hematology (see Section 9.3.4), chemistry including ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and albumin
- Collect blood for hs-CRP at Visit 9 (Week 6), Visit 10 (Week 8), and Visit 11 (Week 10)

- Collect blood samples for serum sarilumab at Visit 10 (Week 8) (see Section 9.1 and the study flow chart Section 1.2)
- Perform urine pregnancy test locally for females who have commenced menstruating at Visit 10 (Week 8)
- Call IVRS to register the visit and get the treatment kit number(s) assigned to each patient along with the dose volume to be administered
- Dispense the IMP to those patients who are at the Dose Regimen 3 Cohort for home injection
- Administer the IMP
  - For those patients or parents or caregivers who are willing and able to perform injections for the patients, the Investigator or delegate will provide the training regarding to preparation and injection of IMP starting from Visit 10 (Week 8). This training must be documented in the patient's study file. The patient or the parent(s)/guardian(s) or the caregiver(s) is allowed to administer the IMP for the patient under the supervision of the Investigator or his/her delegate at Visit 10 (Week 8), Visit 11 (Week 10) and Visit 12 (Week 12) during the core treatment phase. For the subsequent administrations at the extension phase, the patient or the parent(s)/guardian(s) or the caregiver(s) will be allowed to administer the IMP at home and will record information linked to this injection in the diary at the intermediate on-site visits
  - If the patient or the parent(s)/guardian(s) or the caregiver(s) who are unable or who are unwilling to administer IMP, arrangements must be made for a qualified site personnel and/or professional caregiver to administer IMP for the patient
  - Patients should be monitored for at least 30 minutes after IMP administration for any signs or symptoms of a hypersensitivity reaction
- Check local tolerability (see Section 9.3.3)
- Schedule the appointment for the next visit and request the patient to come in fasting condition for Visit 12 (Week 12).

10.1.7 Visit 12 (Week 12)

- Record all concomitant medications use with start date and dose in the patient's e-CRF
- Inquire regarding AEs/SAEs
- Record vital signs including body temperature, BP and HR
- Record patient weight (kg) and height (cm)
- Check Tanner stage (see Appendix F) and menstruation status for female patients
- Check home diary/compliance for Dose Regimen 3 Cohort patients

- Provide home diary to all dose regimen cohort patients to record information pertaining to injections performed at home (date, time, injection location, and any problems) at each intermediate on-site visit. The completed diary will be reviewed at the next scheduled visit
- Perform a complete physical examination including skin, nasal cavities, eyes, ears respiratory, cardiovascular, gastrointestinal, lymphatic, neurological systems, and musculoskeletal systems
- Perform the joint count assessments to note JIA disease manifestations (articular and extra-articular) and assess disease activity (ensure JADAS -27 joints are included)
- Ask the patient/parent(s)/guardian(s) to complete relevant questionnaires: functional ability determined by CHAQ and (parent or guardian)/patient assessment of overall well-being. All questionnaires should be documented in the subject's study file. Each VAS score should be copied on the patient's e-CRF
- Complete the physician global assessment of disease activity
- Perform a tuberculosis risk assessment. In case of suspicion of tuberculosis, refer the patient to a specialist for a complete examination and additional work-up
- Collect blood for hematology (see Section 9.3.4), complete chemistry (including sodium, potassium, chloride, bicarbonate, BUN, glomerular filtration rate, creatinine, creatinine clearance, calcium, phosphate, total protein, albumin, ALT, AST, ALP, total bilirubin, conjugated bilirubin, and unconjugated bilirubin), fasting lipid, hs-CRP, ESR, ANA, and anti-dsDNA
- Collect blood samples for serum sarilumab and antibodies to sarilumab, IL-6 and total sIL-6R (see Section 9.1 and the study flow chart Section 1.2)
- Perform urine pregnancy test locally for female patients who have commenced menstruating
- Call IVRS to register the visit and get the treatment kit number(s) assigned to each patient along with the dose volume to be administered
- Dispense the IMP to those patients who will continue the treatment in the extension phase.
- Administer the IMP for patients who are going to enter the extension treatment phase.
  - Patients should be monitored for at least 30 minutes after IMP administration for any signs or symptoms of a hypersensitivity reaction
- Check local tolerability (see Section 9.3.3)
- Schedule the appointment for the next visit, ie, Visit 13 (Week 16) for patients in the dose-finding and second portions
- Schedule the appointment for the next visit, ie, Visit 15 (Week 24) for patients in the third portion
- Patients who discontinue the study treatment prematurely will be assessed using the procedure planned for the EOT Visit (Visit 27). These patients will be asked to return for an additional PK assessment 2 weeks after the EOT (the additional PK assessment is only

applicable for patients in the dose-finding and second portions) and EOS assessment planned for Visit 28, 6 weeks after the EOT visit. Schedule the appointment for the next PK assessment and EOS visit for those study discontinuation patients, as applicable. Patients discontinuing treatment prematurely during the core treatment phase should continue to return for the study visits as protocol scheduled except the IMP administration.

10.1.8 Visit 88 - Pharmacokinetic (PK) Follow-up Visit (End-of-Treatment [EOT] + 2 Weeks)

Visit 88 is an additional sarilumab PK assessment visit and this visit is not applicable for patients enrolled in the third portion.

In the dose-finding and second portions, if a patient discontinues the study treatment prematurely during the core treatment phase (at or before Week 12), the patient is required to have a PK follow-up visit 2 weeks after the EOT assessment.

- Record all concomitant medication use with start date and dose in the patient's e-CRF
- Inquire regarding AEs/SAEs
- Collect blood samples for serum sarilumab (see Section 9.1 and the study flow chart Section 1.2).

10.1.9 Extension Phase

In the dose-finding and second portions, only patients achieving at least a JIA ACR30 response at Week 12 will be permitted to continue to participate in the extension phase. During the extension phase:

- Patients who were enrolled to the selected dose regimen during the core treatment phase (either during the initial dose-finding portion or directly to the selected dose regimen in the second portion) will continue on the selected dose regimen during the extension phase and will be followed-up as noted in (Section 1.2.2.1)
- Once the selected dose regimen has been determined, patients who were not assigned to the selected dose regimen will have their dose regimen adjusted to the selected dose regimen during the extension phase. Prior to dose adjustment, these patients will complete the assessments as noted in Section 1.2.2.1. After the dose regimen is determined, the patients will have their dose regimen adjusted to the selected dose regimen at the time of their next regular scheduled visit (according to Section 1.2.2.1), which will be considered as the first visit (Visit 101 [Week 0]) as shown in the flow chart in Section 1.2.2.2. These patients will then continue with the assessments as noted in Section 1.2.2.2. All patients will remain on treatment until they have received up to a total of 144 weeks of sarilumab exposure calculated from Visit 12. A table to determine when the last on-treatment visit should occur and the weeks between the last on-treatment visit, and the EOT visit based on when the patient was changed to the selected dose regimen is provided in Table 1. After the last on-treatment visit, patients will be scheduled for the EOT visit (Visit 27) and the EOS visit (Visit 28).

- Patients who are enrolled in the third portion with the selected dose regimen will be followed-up as noted in Section 1.2.2.3.

10.1.9.1 Patients who remain on the current dose (the selected dose regimen) or recruited directly under the selected dose regimen in the second portion

For additional information on the procedures for patients who remain on the current dose (or who are recruited directly under the selected dose regimen [second portion]), see the flow chart in Section 1.2.2.1.

10.1.9.1.1 Visit 13 (Week 16), Visit 14 (Week 20), Visit 15 (Week 24), Visit 16 (Week 32), Visit 17 (Week 40), Visit 18 (Week 48), Visit 19 (Week 60), Visit 20 (Week 72), Visit 21 (Week 84), Visit 22 (Week 96), Visit 23 (Week 108), Visit 24 (Week 120), Visit 25 (Week 132), and Visit 26 (Week 144)

- Record all concomitant medications use with start date and dose in the patient's e-CRF
- Inquire regarding AEs/SAEs
- Check home diary/compliance
- Provide home diary. All patients or their parents or guardians will record information pertaining to injections performed at home (date, time, injection location, and any problems)
- Record vital signs including body temperature, BP, and HR
- Record weight (kg)
- Record patient height at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72), Visit 22 (Week 96), Visit 24 (Week 120), and Visit 26 (Week 144)
- Check Tanner stage and menstruation status at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72), Visit 22 (Week 96), Visit 24 (Week 120), and Visit 26 (Week 144) (see Appendix F)
- Perform a complete physical examination including skin, nasal cavities, eyes, ears respiratory, cardiovascular, gastrointestinal, lymphatic, neurological systems, and musculoskeletal systems at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72), Visit 22 (Week 96), Visit 24 (Week 120), and Visit 26 (Week 144)
- Perform the joint count assessments to note JIA disease manifestations (articular and extra-articular) and assess disease activity (ensure JADAS -27 joints are included) at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72), Visit 22 (Week 96), Visit 24 (Week 120), and Visit 26 (Week 144)
- Ask the patient/parent(s)/guardian(s) to complete relevant questionnaires: functional ability determined by CHAQ and (parent or guardian)/patient assessment of overall well-being at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72), Visit 22 (Week 96), Visit 24 (Week 120), and Visit 26 (Week 144). All questionnaires should be documented in the subject's study file. Each VAS score should be copied on the patient's e-CRF

- Complete the physician global assessment of disease activity at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72), Visit 22 (Week 96), Visit 24 (Week 120), and Visit 26 (Week 144)
- Perform a tuberculosis risk assessment. In case of suspicion of tuberculosis, refer the patient to a specialist for a complete examination and additional work-up
- Perform PPD tuberculin skin test for patients ≤5 years or QuantiFERON-TB test for patients >5 years at Visit 18 (Week 48); Visit 22 (Week 96), and Visit 26 (Week 144). QuantiFERON-TB test will be considered in the younger group of patients (≤5 years) based on the local PPD availability, local regulation for PPD screening, and the Investigator's judgments
- Collect blood for hematology (see Section 9.3.4), chemistry including ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and albumin
- Collect blood for fasting lipids at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72), and Visit 22 (Week 96).
- Collect blood for hs-CRP at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72), Visit 22 (Week 96), Visit 24 (Week 120), and Visit 26 (Week 144)
- Collect blood for ESR at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72), Visit 22 (Week 96), Visit 24 (Week 120), and Visit 26 (Week 144)
- Collect blood for ANA/anti-dsDNA at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72), and Visit 22 (Week 96)
- Collect blood samples for serum sarilumab, antibodies to sarilumab at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72) Visit 22 (Week 96), Visit 24 (Week 120) (see Section 9.1 and the study flow chart Section 1.2)
- Perform urine pregnancy test locally for female patients who have commenced menstruating for each visit
- Call IVRS to register the visit and get the treatment kit number(s) assigned to each patient along with the dose volume to be administered
- Dispense the IMP
- Administer the IMP
  - During the course of the extension phase (starting at Visit 12), the IMP injection dose can be adjusted. Refer Appendix B for injection volume based on the patient's weight
  - Patients should be monitored for at least 30 minutes after IMP administration for any signs or symptoms of a hypersensitivity reaction
- Check local tolerability (see Section 9.3.3)
- Schedule the appointment for the next visit and request patients to come in a fasting condition at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72), Visit 22 (Week 96), Visit 24 (Week 120), Visit 26 (Week 144), and Visit 27 EOT (Week 156).

10.1.9.2 Patients who change to the selected dose regimen

For additional information on the procedures for patients who change to the selected dose regimen, see the flow chart in Section 1.2.2.2.

In this section, "Day" means "Day at this dose," and "Week" means "Week at this dose."

10.1.9.2.1 Visit 101 (Week 0), Visit 102 (Week 2), Visit 103 (Week 4), Visit 104 (Week 6), Visit 105 (Week 8), and Visit 106 (Week 12)

- Tanner stage and menstruation status at Visit 101 (Week 0)
- Review the previous visit's hematology laboratory assessment before the administration of the dose of sarilumab
- Record all concomitant medications use with start date and dose in the patient's e-CRF
- Inquire regarding AEs/SAE
- Record vital signs including body temperature, BP, and HR
- Record weight (kg) at Visit 101 (Week 0), Visit 103 (Week 4), Visit 105 (Week 8), and Visit 106 (Week 12)
- Record height (cm) at Visit 101 (Week 0)
- Perform a complete physical examination including skin, nasal cavities, eyes, ears respiratory, cardiovascular, abdominal, lymphatic, neurological systems, and musculoskeletal systems at Visit 101 (Week 0), Visit 104 (Week 6), and Visit 106 (Week 12)
- Call IVRS to register the visit and get the treatment kit number(s) assigned to each patient along with the dose volume to be administered
- Perform the joint count assessments to note JIA disease manifestations (articular and extra-articular) and assess disease activity. Any abnormalities should be recorded and documented in prior medical/surgical history (ensure JADAS -27 joints are included)
- Ask the patient/parent(s)/guardian(s) to complete relevant questionnaires: functional ability determined by CHAQ and parent/patient assessment of overall well-being. All questionnaires should be documented in the subject's study file. Each VAS score should be copied on the patient's e-CRF
- Complete the physician global assessment of disease activity
- Perform a tuberculosis risk assessment. In case of suspicion of TB, refer the patient to a specialist for a complete examination and additional work-up
- Purified Protein Derivative tuberculin skin test for patients ≤5 years or QuantiFERON-TB test for patients >5 years at Visit 101 (Week 0)
- Collect blood for hematology and complete chemistry profile (see Section 9.3.4) at Visit 101 (Week 0), Visit 102 (Week 2), Visit 103 (Week 4), Visit 105 (Week 8), and Visit 106 (Week 12)
- Collect blood for fasting lipids at Visit 101 (Week 0), Visit 103 (Week 4), and Visit 106 (Week 12)

- Collect blood for hs-CRP from Visit 101 to Visit 106.
- Collect blood for ESR, ANA/anti-dsDNA antibody at Visit 101 (Week 0) and Visit 106 (Week 12)
- Collect blood samples for serum sarilumab (see Section 9.1 and the study flow chart in Section 1.2.2.2) at Visit 101 (Week 0), Visit 102 (Week 2), Visit 103 (Week 4), Visit 105 (Week 8), and Visit 106 (Week 12)
- Collect blood samples for antibodies to sarilumab (see Section 9.1 and the study flow chart in Section 1.2.2.2) at Visit 101
- Perform local urine pregnancy test for the female patients who have commenced menstruation prior to exposure to the IMP at each visit (except Visits 102 [Week 2] and 104 [Week 6])
- Dispense the IMP
- Provide home diary for IMP/compliance
- Administer the IMP
  - Patients should be monitored for at least 30 minutes after IMP administration for any signs or symptoms of a hypersensitivity reaction
- Check local tolerability (see Section 9.3.3)
- Schedule the appointment for the next visit

10.1.9.2.2 Visit 107 (Week 16), Visit 108 (Week 20), Visit 109 (Week 24), Visit 110 (Week 32), Visit 111 (Week 40), Visit 112 (Week 48), Visit 113 (Week 60), Visit 114 (Week 72) Visit 115 (Week 84), Visit 116 (Week 96), Visit 117 (Week 108), Visit 118 (Week 120), and Visit 119 (Week 132)

For detailed information on the procedures for patients who change to the selected dose regimen, see the flow chart in Section 1.2.2.2.

10.1.9.3 Patients enrolled directly under the selected dose regimen in the third portion

For detailed information on the procedures for patients who are recruited directly under the selected dose regimen in the third portion, see the flow chart in Section 1.2.2.3.

10.1.9.3.1 Visit 15 (Week 24), Visit 16.1 (Week 36), Visit 18 (Week 48), Visit 19 (Week 60), Visit 20 (Week 72), Visit 21 (Week 84)

- Record all concomitant medications use with start date and dose in the patient's e-CRF
- Inquire regarding AEs/SAEs
- Check home diary/compliance
- Provide home diary. All patients or their parents or guardians will record information pertaining to injections performed at home (date, time, injection location, and any problems)

- Record vital signs including body temperature, BP, and HR
- Record weight (kg)
- Record patient height at Visit 15 (Week 24), Visit 18 (Week 48), and Visit 20 (Week 72)
- Check Tanner stage and menstruation status at Visit 15 (Week 24), Visit 18 (Week 48), and Visit 20 (Week 72) (see Appendix F)
- Perform a complete physical examination including skin, nasal cavities, eyes, ears respiratory, cardiovascular, gastrointestinal, abdominal, lymphatic, neurological systems, and musculoskeletal systems at Visit 15 (Week 24), Visit 18 (Week 48), and Visit 20 (Week 72)
- Perform the joint count assessments to note JIA disease manifestations (articular and extra-articular) and assess disease activity (ensure JADAS -27 joints are included) at Visit 15 (Week 24), Visit 18 (Week 48), and Visit 20 (Week 72)
- Ask the patient/parent(s)/guardian(s) to complete relevant questionnaires: functional ability determined by CHAQ and (parent or guardian)/patient assessment of overall well-being at Visit 15 (Week 24), Visit 18 (Week 48), and Visit 20 (Week 72). All questionnaires should be documented in the subject's study file. Each VAS score should be copied on the patient's e-CRF
- Complete the physician global assessment of disease activity at Visit 15 (Week 24), Visit 18 (Week 48), and Visit 20 (Week 72)
- Perform a tuberculosis risk assessment. In case of suspicion of tuberculosis, refer the patient to a specialist for a complete examination and additional work-up
- Perform PPD tuberculin skin test for patients ≤5 years or QuantiFERON-TB test for patients >5 years at Visit 18 (Week 48); QuantiFERON-TB test will be considered in the younger group of patients (≤5 years) based on the local PPD availability, local regulation for PPD screening, and the Investigator's judgments
- Collect blood for hematology (see Section 9.3.4), chemistry including ALT, AST, ALP, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and albumin
- Collect blood for fasting lipids at Visit 15 (Week 24) and Visit 18 (Week 48)
- Collect blood for hs-CRP at Visit 15 (Week 24), Visit 18 (Week 48), and Visit 20 (Week 72)
- Collect blood for ESR at Visit 15 (Week 24), Visit 18 (Week 48), and Visit 20 (Week 72)
- Collect blood for ANA/anti-dsDNA at Visit 15 (Week 24) and Visit 18 (Week 48)
- Collect blood samples for serum sarilumab, antibodies to sarilumab at Visit 15 (Week 24), Visit 18 (Week 48), Visit 20 (Week 72) (see Section 9.1 and the study flow chart Section 1.2)
- Perform urine pregnancy test locally for female patients who have commenced menstruating for each visit

- Call IVRS to register the visit and get the treatment kit number(s) assigned to each patient along with the dose volume to be administered
- Dispense the IMP
- Administer the IMP
  - During the course of the extension phase (starting at Visit 12), the IMP injection dose can be adjusted. Refer Appendix B for injection volume based on the patient's weight
  - Patients should be monitored for at least 30 minutes after IMP administration for any signs or symptoms of a hypersensitivity reaction
- Check local tolerability (see Section 9.3.3)
- Schedule the appointment for the next visit and request patients to come in a fasting condition at Visit 15 (Week 24), Visit 18 (Week 48)

Visits 13, 14, 16, 17, 22, 23, 24, 25, and 26 are not applicable for patients enrolled in the third portion.

10.1.10 Visit 27: End-of-Treatment visit

Visit 27 (EOS) will be Week 156 for patients enrolled in the dose-finding and second portions and Week 96 for patients enrolled in the third portion.

- Record all concomitant medications used with start date and dose in the patient's e-CRF
- Inquire regarding AEs/SAEs
- Record vital signs including body temperature, BP and HR
- Record patient weight (kg) and height (cm)
- Check Tanner stage and menstruation status for female patients (see Appendix F)
- Check home diary/compliance
- Perform a complete physical examination including skin, nasal cavities, eyes, ears respiratory, cardiovascular, gastrointestinal, lymphatic, neurological systems, and musculoskeletal systems
- Perform the joint count assessments to note JIA disease manifestations (articular and extra-articular) and assess disease activity (ensure JADAS -27 joints are included)
- Ask the patient/parent(s)/guardian(s) to complete relevant questionnaires: functional ability determined by CHAQ and (parent or guardian)/patient assessment of overall well-being. All questionnaires should be documented in the subject's study file. Each VAS score should be copied on the patient's e-CRF
- Complete the physician global assessment of disease activity
- Perform a tuberculosis risk assessment. In case of suspicion of tuberculosis, refer the patient to a specialist for a complete examination and additional work-up

- Collect blood for hematology (see Section 9.3.4) and complete chemistry (including sodium, potassium, chloride, bicarbonate, BUN, glomerular filtration rate, creatinine, creatinine clearance, calcium, phosphate, total protein, albumin, ALT, AST, ALP, total bilirubin, conjugated bilirubin, and unconjugated bilirubin; see Section 9.3.4)
- The IL-6 and total sIL-6R will be measured for patients who discontinue the study treatment prematurely during the core treatment phase
- Collect blood for hs-CRP, ESR, serum sarilumab, and antibodies to sarilumab
- Collect blood for fasting lipids and ANA/anti-dsDNA only for patients who discontinue prematurely before Week 96 (for the dose-finding and second portion)/Week 48 (for the third portion)
- Perform urine pregnancy test for female patients who have commenced menstruating
- Call IVRS to notify the patient's status (EOT)
- There is no IMP administration at this visit
- Check local tolerability (for patients who change to the selected dose; see Section 9.3.3)
- Schedule the appointment for the post-treatment follow-up visit of Visit 28 (EOT + 6 weeks).

Post-treatment safety follow-up (Visit 28; 6 weeks after EOT assessment, EOT+6 weeks)

10.1.11 Visit 28 (End-of-Treatment [EOT] +6 weeks) End-of-Study Visit: Post-treatment follow-up

- Record all concomitant medications use with start date and dose in the patient's e-CRF
- Inquire regarding AEs/SAEs
- Record vital signs including body temperature, BP and HR
- Record patient weight (kg)
- Check Tanner stage (see Appendix F) and menstruation status for female patients
- Perform a tuberculosis risk assessment. In case of suspicion of tuberculosis, refer the patient to a specialist for a complete examination and additional work-up
- Collect blood for serum sarilumab and antibodies to sarilumab
- Call IVRS to notify the patient's status (study completion).

Note: Post-treatment follow-up visit is also applied at 6 weeks after EOT visit for those patients who permanently discontinue the study treatment.

10.2 DEFINITION OF SOURCE DATA

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

All evaluations that are reported in the e-CRF must be supported and identified by appropriate source documentation related but not limited to:

- Patient chart
- Number of joints with active arthritis
- Number of joints with limitation of motion
- Physician's global assessment of disease activity
- Parent/patients assessment of overall well-being
- Childhood Health Assessment Questionnaire
- Home injection diaries (if applicable), serum sarilumab diary (when samples are collected at home) and patients user instruction
- Laboratory assessment including chest X-ray
- The e-CRF will be verified against the source documentation to ensure that all data are captured accurately.

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

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

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation decided by the Investigator corresponds to more than one injection not administered to the patient.

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. For laboratory abnormalities, Investigator will refer to Appendix G for the stopping rules. Re-initiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF (see Appendix G for the stopping rules).

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

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

A temporary discontinuation of IMP that is greater than 31 days could be considered permanent if a significant impact on the efficacy has been identified.

10.3.3 List of criteria for permanent treatment discontinuation

The patient or the parent(s) or the legal guardian(s) may withdraw the patient from treatment with the IMP if they decide to do so at any time and irrespective of the reason. Based on the Investigator's judgment, the patient could be discontinued from the study treatment once his/her condition requires the treatment with prohibited medications (starting new DMARDs, significant increase in glucosteroids or considering other biologic therapy, etc). All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

Investigational medicinal product will be permanently discontinued in case of the following events (refer to Section 10.6 for details):

- Clinical significant infections such as opportunistic infections (see Appendix I) or active tuberculosis
  - The diagnosis of tuberculosis can be made either on symptoms or on a chest radiograph suggestive of active tuberculosis. Patients should be referred to appropriate medical specialists and whenever possible, skin PPD test or blood QuantiFERON-TB test should be performed and the results should be recorded in the e-CRF
  - Culture positive for non-TB mycobacteria
  - The patient is at risk through close contact with a person with active tuberculosis and the patient refuses to undergo tuberculosis evaluation
- Symptoms of systemic hypersensitivity or anaphylactic reactions
- Significant laboratory abnormalities
  - ALT >5 x ULN or ALT >3 x ULN with concomitant total bilirubin >2 x ULN (unless patient with documented Gilbert's Syndrome)
  - neutrophil count <1000/mm^3 (Grade 3 or 4 neutropenia) with evidence of infection
  - platelet count <50 000/mm^3, or platelet count <100 000/mm^3 with evidence of bleeding
- Acute renal failure (refer to Appendix G)
- Pregnancy in female participant

- Use of any biologic DMARDs other than IMP
- Any AEs, per Investigator's judgment that may jeopardize the patient's safety.

Any abnormal laboratory value that is close to the values described in Appendix G should be immediately rechecked for confirmation. No dose will be given until the results of the confirmation laboratory tests are received. No decision by the Investigator or Sponsor should be made to permanently discontinue the IMP for the concerned patient until the results of the confirmation laboratory test are received.

10.3.4 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 early termination visit and the post-treatment visit, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

Patients discontinuing treatment prematurely before 12 weeks should continue to be followed according to the study flow chart, with the exception of treatment dispensing and administration. An additional PK sampling is required 2 weeks after the EOT assessment.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure for the EOT visit, including a sample for determination of sarilumab concentration (bound and functional) and antibodies to sarilumab, if appropriate. The patients will be asked to return for the EOS assessments 6 weeks after the EOT assessment. This EOS visit will be applicable to all the patients in both the core treatment phase and the extension phase.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients or parent(s) or the guardian(s) may withdraw the patient 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 for the End-of-Treatment visit including serum sarilumab (PK) level and anti-sarilumab antibodies evaluation.

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

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered. Patients who have withdrawn from the study cannot be re-entered (treated) in the study. Their inclusion and treatment numbers must not be reused.

If possible, the patients should be assessed using the procedures defined above.

The patient/parent(s)/guardian(s) who withdraw consent should be explicitly asked about the contribution of possible AEs. Preferably the patient should withdraw consent in writing and, if the patient or the parent(s)/guardian(s) refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

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

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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

10.4.1.2 Serious adverse event

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

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

  Note: The term "life threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

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

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

10.4.1.3 Adverse event of special interest

An AESI is an AE (serious or non serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor are required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study. AESIs will be flagged in the database using search criteria (see Section 10.4.4 for AESI reporting).

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NonIMP, spanning from the signature of the ICF until the EOS as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-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.

- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- Patients who experience an ongoing SAE or an AESI 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 EOS as defined by the protocol for that patient.
- Laboratory results and vital sign values are to be recorded as AEs only if:
  - Associated with symptoms, and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.

10.4.3 Instructions for reporting serious adverse events

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

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

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

10.4.4 Guidelines for reporting adverse events of special interest

10.4.4.1 Reporting of adverse events of special interest

For AESIs, the Sponsor will be informed immediately (ie, within 24 hours), as per the SAE notification instructions described in Section 10.4.3 and Table 7 even if not fulfilling a seriousness criterion, using the corresponding pages in the e-CRF (to be sent) or screens in the e-CRF. The following is the list for AESIs for this study:

- Clinically significant infections including:
  - Opportunistic infections (refer to Appendix I) (Note: Candidiasis – only systemic and/or extensive mucocutaneous cases of candidiasis)
  - Active/latent tuberculosis or initiation of medications for suspected tuberculosis
- Anaphylaxis fulfilling the criteria in the Appendix H
- Gastrointestinal
  - Perforation
  - Diverticulitis
- The following laboratory abnormalities:
  - Alanine aminotransferase increase leading to permanent discontinuation
  - Grade 4 neutropenia (>10 days after the initial IMP administration) or any neutropenia leading to permanent discontinuation
  - Thrombocytopenia leading to permanent discontinuation
- Pregnancy (adolescent):
  - Pregnancy occurring in a female patient included in the clinical trial (as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP) will be recorded as an AESI in all cases and reported to the sponsor immediately (within 24 hours of knowledge). It will be qualified as an SAE only if it fulfills the SAE criteria.
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined, or as permitted according to applicable local regulations.
- Symptomatic overdose with IMP
  - 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 during an interval of less than 11 days for q2w administrations and less than 6 days for weekly administration. Symptomatic overdose is defined as an AESI and reported the sponsor immediately (within 24 hours of knowledge), following the same process as described for the SAEs. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms. Overdose without symptoms should be reported as an AE.

Table 7 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case report form completion		
			AE form	Safety complementary form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
All Serious Adverse Events	Expedited (within 24 hours of knowledge)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	As needed for select AESI
AESI	Expedited (within 24 hours of knowledge)	The following AE defined in Section 10.4.4.1			
		• Clinically significant infections including: - Opportunistic infections (see list in Appendix I) (Note: Candidiasis – only systemic candidiasis and extensive cases) - Active/latent TB or initiation of medications for suspected TB	Yes	Yes	Yes
		• Anaphylaxis fulfilling the criteria in Appendix H	Yes	Yes	Yes
		• Gastrointestinal perforation and diverticulitis	Yes	Yes	No
		• ALT increase leading to permanent discontinuation	Yes	Yes	Yes
		• Grade 4 neutropenia (>10 day after the initial IMP administration) or any neutropenia leading to permanent discontinuation	Yes	Yes	Yes
		• Thrombocytopenia leading to permanent discontinuation	Yes	Yes	Yes
		• Pregnancy of a female adolescent patient/or partner of a male adolescent patient participating in the study	Yes	Yes	Yes
		• Symptomatic overdose with IMP	Yes	Yes	Yes

Event category	Reporting timeframe	Specific events in this category	Case report form completion		
			AE form	Safety complementary form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Any laboratory, vital sign 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.	Routine	Report specific abnormality	Yes	No	No

Abbreviations: AE = adverse event, AESI = adverse event of special interest, ALT = alanine aminotransferase, IMP = investigational medicinal product, SAE = serious adverse event, TB = tuberculosis
Reminder: Safety Complementary Forms should be completed for all SAEs and AESIs.

10.4.5 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix G. Evaluation and management of these laboratory abnormalities may include, but are not limited to those listed in the appendices. Investigators should assess the patient clinically and further evaluate the patient with assessments beyond those listed the appendices, if needed, according to his/her best clinical judgment as well.

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

- Neutropenia
- Thrombocytopenia
- Alanine aminotransferase increase
- Acute renal insufficiency

NOTE: In some clinical trials these laboratory abnormalities can be considered as AESIs (see Section 10.4.4.1).

10.5 OBLIGATIONS OF THE SPONSOR

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

- All SAEs that are both unexpected and at least reasonably related to the IMP (suspected unexpected serious adverse reaction [SUSAR]), to the Health Authorities, Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) as appropriate and to the Investigators
- All SAEs that are expected and at least reasonably related to the IMPs to the Health 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 unexpected.

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

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

10.6 SAFETY INSTRUCTIONS

10.6.1 Infections

Biologics including tumor necrosis factor (TNF) antagonists and tocilizumab (another IL-6R antagonist similar to sarilumab) have been associated with an increased risk of infection, including black box warnings for serious infections leading to hospitalization or death. In Phase 2 sarilumab studies in adults, the most commonly reported TEAEs were infections (mostly nonserious upper respiratory and urinary tract infections). In the ongoing phase 3 program, clinically significant infections including life threatening sepsis, have been reported, some notably associated with minor trauma. As a precautionary measure, Investigators should carefully follow any signs of infection with particular care to identify potential infective complications in immune-suppressed individuals where superficial skin wounds or abrasions may lead to serious infections including necrotizing fasciitis and/or sepsis.

Any infection should be reported by the Investigator as an AE and a corresponding e-CRF form should be filled in. If possible, culture should be performed to identify the type of infection. The type of infection should be listed in the e-CRF form. Treatment with antibiotics, if any, should be recorded including the route of administration. Clinically significant infections including opportunistic infections are AESIs and should be reported accordingly (Section 10.4.4.1). The IMP should be discontinued in case of suspicion of a clinically significant infection and a complete diagnosis work-up should be performed.

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

- A clinical examination and history will be performed at every visit to assess any signs and symptoms of TB or contact with a patient with active TB.
- Purified Protein Derivative (PPD) skin test or QuantiFERON-TB blood test will be performed at the Screening visit and can be repeated at any time during the course of the studies in case of suspicion of TB (Refer to E 13 for the details)
- In case of suspicion of TB, the Investigator must refer the patient to a specialist for a complete examination. The IMP should be discontinued until TB is ruled out.

Chest X-ray: A standard posterior-anterior chest X-ray (lateral view is also recommended but not required) may be recommended when deemed necessary based on the Investigator's judgment or in line with local guidelines for TB screening prior to initiating a biologic therapy for JIA patients who haven't had a chest X-ray performed within 3 months prior to Baseline.

10.6.2 Liver function tests

Please refer to Section 10.4.4 for LFT abnormalities to be reported as AESI.

The Sponsor relies on the Investigator's judgment for adapting concomitant medication in case of LFT abnormalities.

In the present protocol, in order to closely follow liver function tests, assessment of ALT, AST, ALP, and bilirubin (total, conjugated) are performed per specifications on the study flow charts (sec flow chart Section 1.2 and Appendix G for the general guidance for the follow-up of ALT elevation).

10.6.3 Neutrophils

For all patients, a hematology test must be performed and the results must meet eligibility criteria prior to the enrolment.

For all subsequent visits, in order to prevent the administration of IMP in patients at risk for severe neutropenia, the hematology test will be performed and the results will be reviewed. Please refer to Appendix G for guidance on the follow-up of neutropenia and refer to Section 10.4.4.1 criteria for reporting neutropenia as AESI or SAE.

10.6.4 Platelets

For all patients, a hematology test must be performed and the results must meet eligibility criteria prior to the enrolment.

For all subsequent visits, in order to prevent the administration of IMP in patients at risk for thrombocytopenia, the hematology test will be performed and the results will be reviewed. Please refer to Appendix G for guidance on the follow-up of thrombocytopenia and refer to Section 10.4.4.1 criteria for reporting thrombocytopenia as AESI or SAE.

10.6.5 Systemic hypersensitivity reactions/anaphylaxis

Severe systemic hypersensitivity reactions (in rare cases, fatal anaphylaxis) have been reported with biologics. Infrequent, mild to moderate, systemic hypersensitivity reactions have been observed with sarilumab. The patient should be monitored for 30 minutes after the IMP injection when given at the study site. Also patient should be advised, when IMP is administered at home, to self-monitor for potential signs and symptoms that may suggest a hypersensitive reaction for 30 minutes after administration. Any problems should be documented in the patient's home diary or in the medical notes and reported as AE. In case of systemic hypersensitivity reaction, the IMP should be discontinued and those events meeting seriousness criteria (eg, hospitalization, life threatening); see Section 10.4.1.2 should be reported as SAEs. Appendix H defines clinical criteria for diagnosing anaphylaxis. If clinical criteria for anaphylaxis are met, appropriate treatment should be administered immediately and the event should be reported as a SAE.

For Germany only: After the first IMP administration the patient has to be monitored for at least 1 hour to assess tolerability.

10.6.6 Diverticulitis and Gastrointestinal Perforation

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

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

Gastrointestinal perforation is an AESI to be reported as SAE (see Section 10.4.3 and Section 10.4.4.1) Confirmed gastrointestinal ulceration without perforation and diverticulitis should be reported as AESI (Section 10.4.3).

10.6.7 Management of dyslipidemia

Patients treated with tocilizumab have been observed to have increased elevations of all lipid parameters, including low density lipoprotein (LDL) cholesterol. A similar finding has been observed for sarilumab. The potential for dyslipidemia in pcJIA patients treated with IL-6R antagonists is unknown. Patients who are found to have dyslipidemia during the course of the study should refer National Cholesterol Education Program (NCEP) Expert Panel Report on Blood Cholesterol levels in Children and Adolescents and refer to applicable local guideline for the standard care of treatment (24).

10.6.8 Acute renal failure

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

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

[redacted]

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as patients meeting the inclusion criteria and having a signed informed consent/assent (as applicable).

Included patients consist of all patients with a signed ICF who have had a treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used.

For patient study status, the total number of patients in each of the following categories will be presented in the CSR using a flowchart diagram or summary table:

- Screened patients
- Screen failure patients
- Included patients

- Included but not treated patients
- Included and treated patients
- Patients completing the initial 12-week core treatment phase
- Patients completing the study treatment per protocol
- Patients who did not complete the study treatment period as per protocol
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation
- Patients entering the extension phase
- Status at last study contact.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

The **efficacy population** consists of all included patients who receive at least 1 dose of sarilumab. All patients should be followed at least to the end of the 12-week study treatment period and will be analyzed according to the treatment that they actually receive.

11.3.2 Safety population

Safety population: the included population who actually received at least 1 dose or part of a dose of the IMP, analyzed according to the treatment actually received.

In addition:

- Patients for whom it is unclear whether they took the study medication will be included in the safety population according to the assigned treatment.
- In case a patient receives 1 or more incorrect doses of sarilumab other than the one assigned, the dose regimen allocation for as-treated analysis will be the dose regimen in which he/she was treated for the longest duration.

11.3.3 Pharmacokinetic, pharmacodynamics, and immunogenicity population

The PK population will consist of all patients in the safety population with at least one post-dose, nonmissing serum concentration value. The PD population will consist of all patients in the safety population with at least one post-dose biomarker assessment. The ADA population will consist of all patients in the safety population with at least one post-dose, evaluable ADA sample. Patients will be analyzed according to the treatment actually received.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual IMP dose regimen, overall and within each weight group, using the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure, and actual dose information.

The duration of sarilumab exposure is defined as: last dose date - first dose date+ 14 days for Dose Regimens 1 and 2 (+ 7 days for Dose Regimen 3). These calculations are regardless of unplanned intermittent discontinuations. Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum) and by categories. Additionally, the cumulative duration of treatment exposure, defined as the sum of patients' duration of treatment exposure and expressed in patient years, will be provided.

11.4.1.2 Compliance

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

Percentage of compliance for a patient will be defined as the number of administrations that the patient was compliant divided by the total number of administrations that the patient was planned to take on or before the last dose date during the treatment epoch.

Treatment compliance percentages will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum), along with a summary of the percentage of patients whose compliance is <80%. In addition, patients with the wrong dose will be summarized.

Overdose is defined as administering 2 or more sarilumab doses in less than 11 calendar days for q2w dosing and in less than 6 calendar days for qw dosing. Symptomatic overdose will be reported as an AESI. More generally, dosing irregularities will be listed.

11.4.2 Analyses of efficacy endpoints

See Section 9.3.4. Efficacy is considered as secondary in this study. Efficacy data will be summarized descriptively. The approach to handle the dose-adjustment in the efficacy analyses will be detailed in the statistical analysis plan.

11.4.2.1 Analysis of primary efficacy endpoint(s)

Analysis of JIA ACR30 response is provided in this study section.

Patients achieving JIA ACR30 response for each dose regimen cohort, overall, and by weight group will be summarized by visit using counts, proportions and 95% CIs. All observed data, while the patient remains on treatment will be included in this analysis. No missing data will be imputed. Additionally, for the summaries on the JIA ACR 30 responses during the 12-week core treatment phase, several different approaches will be used for the handling of treatment discontinuations and missing data.

Non responder imputation:

In general, number of joints with active arthritis, number of joints with limited range of motion, and at least 3 of the remaining 4 ACR components at Baseline and a time point are required to determine responder status.

In this method of missing data handling, the data collected after treatment discontinuation will be set to missing. No imputation of missing post baseline values will be performed. Responder status will be determined using available data and patients will automatically become non responders for all time points beyond the time point they discontinued study treatment or for which there is insufficient data.

LOCF approach:

In this method of missing data handling, the missing data will be imputed using the LOCF procedure from the point of treatment discontinuation for all 6 ACR components for all visits post that point. Responder status will be determined using the imputed data.

In this approach, patients with insufficient data after imputation (ie, number of joints with active arthritis, number of joints with limited range of motion, and at least 3 of the remaining 4 ACR components) at baseline and a time point will be considered as non responders at that time point.

As observed including post discontinuation follow-up:

All observed data up to Week 12, including those collected after treatment discontinuation, will be included in this analysis. No missing data will be imputed.

Subgroup analyses:

No additional subgroup summaries are planned for the efficacy.

11.4.2.2 Analyses of secondary efficacy endpoints

Juvenile idiopathic arthritis ACR30 core set variable scores and changes from baseline for each dose regimen cohort and weight group will be summarized by visit using means, standard errors, and corresponding 95% CIs. Juvenile idiopathic arthritis ACR30 response using ESR instead of hs-CRP will be summarized using the same methods as for the primary efficacy endpoint.

ACR50/70/90/100 will be summarized using the approaches as described above for ACR30. Overall score and change from baseline in JADAS-27 will be summarized by visit (including number, mean, and standard error, SD, median, minimum, and maximum) for each dose regimen cohort and weight group (if possible).

11.4.2.3 Multiplicity considerations

No formal hypothesis testing will be performed in this study.

11.4.3 Analyses of safety data

Safety data will be summarized descriptively. The summary of safety results will be presented by dose regimen. Further subdivision by weight group will be performed only for selected parameters given the small sample size. Additional methods including the approach to handle the dose-adjustment in safety analyses, safety analyses by time periods, and the exposure-adjusted analyses on safety events will be detailed in the statistical analysis plan.

The safety analysis will be based on the reported AEs and other safety information, such as clinical laboratory data, vital signs, etc. Safety and acceptability assessments (local tolerability) are the primary objectives of the extension parts of the studies (see Section 9.3).

All safety analyses will adhere to Sanofi "Guideline for the Analysis and Reporting of Safety Data from Clinical Trials."

Observation period

The observation period will be divided into 5 epochs: Screening, Treatment in core period, Treatment in extension period, Follow-up, and Post-study (defined below):

- The **Screening** epoch is defined as the time from the signed informed consent date up to the time prior to the first dose of IMP.
- The **Core-treatment** epoch is defined as the time from the first dose of IMP to last dose in the core treatment phase + 13 days (or + 6 days for patients on weekly dosing), or first dose of IMP in the extension period for patients who enter the extension phase.
- The **Extension treatment** epoch is defined as the time from first dose of IMP in extension period to last dose of IMP in extension period + 13 days (or + 6 days for patients on weekly dosing). Only patients who enter the extension period have the **Extension treatment** epoch.
- The **Follow-up treatment** epoch is defined as the time from the EOT epoch (ie, the end of **core-treatment** epoch for patients not entering in the extension period; or the end of the **extension treatment** epoch for patients who enter the extension period) to last dose of IMP + 60 days.
- The **Post-study epoch** is defined as the time after the last dose of IMP + 60 days. The rationale of having "last dose of IMP + 60 days" as the end of **follow-up** epoch is to capture the events observed within approximately 5 half-lives of the last IMP.

The entire TEAE period includes the **core treatment**, **extension treatment** (only applicable for patients who enter the extension), and **follow-up** epochs. The TEAE period in the core treatment phase includes **core-treatment** epoch for patients who enter the extension, and includes **core-treatment** and **follow-up** epochs for patients not entering the extension.

All safety analyses will be performed on the safety population, unless otherwise specified, using the following common rules:

- The baseline value is defined as the last available value prior to the first dose of the study medication.
- 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 and vital signs.
- The PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the TEAE period by dose regimen on the safety population.
- For quantitative safety parameters based on laboratory measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and dose regimen. Summaries will include the endpoint value. The endpoint value is commonly defined as the value collected at the same day/time of the last dose of investigational product. If this value is missing, this endpoint value will be the closest one prior to the last dose intake.
- Analyses of the safety variables will be essentially descriptive and no systematic between-group testing is planned.

Adverse events

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

All treatment-emergent AESIs will be summarized by AESI category and PT, showing number (%) of patients, sorted by decreasing incidence of PT within each AESI category (see Section 10.4.4.1).

Death

The incidence of death, if applicable, will be generated on the safety population

Number (%) of patients who died by study period (on-treatment, during follow-up or post-study):

- Death in included but not treated patients
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC, HLGT, HLT and PT, and by primary SOC and PT, showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT for the 4-level summary.

Clinical laboratory evaluations

The summary statistics (including number, mean, median, standard deviation, minimum, and maximum) of all laboratory variables (laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post baseline time point, endpoint) by dose regimen. This section will be organized by biological function.

The incidence of PCSAs and abnormal laboratory values at any time during the TEAE period will be summarized by biological function and dose regimen.

For lipids, the NCEP APTIII classification will be used for the baseline.

The incidence of neutropenia, thrombocytopenia, and lymphopenia by maximal grade will be summarized.

Hepatic disorders

The liver function tests (LFTs), namely AST, ALT, ALP, and total bilirubin are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by dose regimen for each parameter. The proportion of patients with PCSA values at any post baseline visit may be displayed by duration of exposure for each dose regimen cohort.

A graph of the 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 3x ULN for ALT and a horizontal line corresponding to 2x ULN for total bilirubin.

The normalization (to <1 ULN) or return to baseline (in case of baseline is >ULN) of elevated LFTs will be summarized by categories of elevation (>3 ULN, >5 ULN, >10 ULN, >20 ULN for ALT and AST; >1.5 ULN for ALP; and >1.5 ULN and >2 ULN for total bilirubin) with the following categories of normalization: 1) normalized on-treatment; 2) continued into extension study (for initial analysis of 12-week core treatment phase); 3) normalized after last dose; 4) last value not normal. The labs measured during the post-study period will be considered in the analysis of normalization. Note that a patient is counted only once under the maximum elevation category.

Vital signs

The summary statistics (including number, mean, median, standard deviation, minimum, and maximum) of all vital signs variables (vital signs values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post baseline time point, endpoint) by dose regimen. The average of the two systolic blood pressure (SBP) and the two diastolic blood pressure (DBP) readings for a patient at a particular visit will be used for analysis.

The incidence of PCSAs at any time during the TEAE period will be summarized by dose regimen.

11.4.4 Analyses of pharmacokinetic and pharmacodynamics variables

Pharmacokinetic (PK) analyses will be performed using the PK population via pooling all available data.

Serum trough concentrations of functional sarilumab will be summarized using descriptive statistics (including number, arithmetic and geometric means, standard deviation, standard error of the mean (SEM), CV, minimum, median, and maximum) by dose, overall and by weight group, for each visit. The samples will be considered non eligible for these analyses if the previous dosing time is <11 days or >17 days before the sampling time for q2w regimens; <5 days or >9 days before the sampling time for qw regimens. Concentrations below the lower limit of quantification (LLOQ) will be set to zero for samples at predose (Week 0). Other concentrations below LLOQ will be replaced by LLOQ/2. Semi log plots of concentration over time will also be provided (no value at time 0). Serum concentrations of functional sarilumab will be summarized using descriptive statistics mentioned above by immunogenicity status for each dose at each visit (see Section 9.1 and Section 9.7).

A PopPK model will be developed using [redacted] to describe the PK profile of sarilumab. A PopPK model will be used to estimate population and individual PK parameters, the sources of PK variability and assess the influence of covariates on PK parameters. The potential covariates to be evaluated in the PopPK analysis include [redacted] The predicted individual sarilumab PK exposure (C_{max} and $AUC_{0-\tau}$) following the first dose will be summarized using descriptive statistics by dose and weight group. PopPK results may be presented in a separate document from the CSR.

Serum concentrations of IL-6, total sIL-6Rα and hs-CRP will be summarized using descriptive statistics (including number, arithmetic and geometric means, standard deviation, standard error of the mean [SEM], CV, minimum, median, and maximum) by dose and weight group for each visit (Section 9.1 and Section 9.7).

[redacted]

11.4.6 Analysis of immunogenicity variables

At each sample time, the result of the ADA assay will be categorized as either positive or negative, and in the case of a positive result will be further characterized as either neutralizing or non-neutralizing.

ADA-positive patient is defined as a patient with at least 1 treatment-emergent or treatment-boosted ADA-positive sample during the TEAE period, where

- Treatment-emergent ADA-positive patient is defined as a patient with non-positive assay (meaning negative or missing) response at baseline but with a positive assay response during the TEAE period
- Treatment-boosted ADA-positive patient is defined as a patient with a positive ADA assay response at baseline and with at least a 4-fold increase in titer compared to baseline during the TEAE period.

ADA-negative patient is defined as a patient without a treatment-emergent or treatment-boosted ADA-positive sample during the TEAE period.

ADA prevalence and titer

The following summary will be provided based on the ADA population:

- Number (%) of patients with an ADA-positive sample at baseline
  - Number (%) of neutralizing antibody
  - Number (%) of non-neutralizing antibody
  - The summary statistics (including number, median, Q1, Q3, minimum, and maximum) of the titer for the baseline ADA-positive patients
- Number (%) of patients with an ADA-negative sample at baseline.

ADA incidence and titer

The following summary will be provided based on the ADA population during the TEAE period:

- Number (%) of ADA-negative patients
- Number (%) of ADA-positive patients
  - Number (%) of patients with neutralizing antibody
  - Number (%) of patients with non-neutralizing antibody
- Number (%) of treatment-emergent ADA-positive patients
  - The summary statistics (including number, median, Q1, Q3, minimum, and maximum) of the peak post baseline titer for treatment-emergent ADA-positive patients
- Number (%) of treatment-boosted ADA-positive patients
  - Number (%) of patients with neutralizing antibody

- Number (%) of patients with non-neutralizing antibody.

In addition, number (%) of patients with ADA-positive or negative response at each visit will be summarized by dose.

ADA and PK

By visit descriptive summary of serum concentration of sarilumab will be provided by ADA patient classification (positive or negative) for each dose regimen.

Scatter plots of serum concentration versus visit will also be provided by ADA classification (positive or negative) and dose regimen.

11.5 INTERIM ANALYSIS

Ongoing review of safety data will be performed by an independent DMC (Section 6.2). The timing of DMC reviews will be detailed in the DMC charter. An internal DEC will review accumulating safety, PK, PD, and efficacy data, according to the timing and rules described in Section 6.1.2.

The first formal interim analysis will be performed once sufficient Week 12 data have been observed from the dose-finding portion of the study to allow a selection of a dose regimen for more detailed investigation. If the enrollments for Weight Group B are not completed within a similar time frame as that for weight Group A, the dose selection for weight Group A will be done separately from the dose selection for weight Group B, ie, two separate data analyses will be needed.

The second interim analysis will be performed approximately 1 year from the time every patient enrolled in the dose-finding and second portions has received the selected dose regimen (either new enrolled patients or patients already in the extension phase). Only patients enrolled in the dose-finding and second portions will be included in this interim analysis.

The third interim analysis will occur approximately 1 year from the time the last patient is enrolled in the third portion.

The final database lock will occur approximately 4 weeks after the last patient has completed the EOS visit.

The primary objective is PK estimation and there is no formal hypothesis testing, thus there are no statistical implications for the summary and reporting of the final data at the conclusion of the extension.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

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

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Sub-investigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for GCP, all applicable laws, rules and regulations. This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient who is ≥6 years and parent(s) or legal guardian(s) of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All patient(s)/parent(s)/legal guardian(s) should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

It is the responsibility of the Investigator or designee (if acceptable by local regulations) to obtain written informed assent from each patient ≥6 years of age (or above an age determined by the IRB/IEC and in according with the local regulations and requirements) and written informed consent from each patient's parent(s) or legal guardian(s) prior to the patient's participation in the study. The written informed consent should be signed and dated by the patient's parent(s) or legal guardian(s) and the same Investigator or designee.

Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the Investigator must document the reason the other parent or guardian did not sign. The patient may also be required to sign and date the ICF as determined by the IRB/IEC and in accordance with the local regulations and requirements.

- Patient(s)/parent or legal guardian(s) who can write but cannot read will have the assent/consent form read to them before writing their name on the form

- Patients/parent or legal guardian who can understand but who can either write nor read will have the informed assent/consent form read to them in presence of an impartial witness, who will sign and date the assent/consent form to confirm that informed consent was given.

The original assent/consent form must be retained by the Investigator as part of the patient's study record and a copy of the signed assent/consent form must be given to the patient/patient's parent(s) or legal guardian(s).

The patient's general practitioner (family doctor) if any and if the parents/legal guardian and patient agree will be informed by the Investigator of the patient's participation in this study. Information regarding the study treatment will be sent to the family doctor.

The informed assent/consent form used by the Investigator must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion. In relation with the population of patients exposed in the trial, ie, pediatric/minor patients, the IRB/IEC should ensure proper advice from specialists with pediatrics expertise (competent in the area of clinical, ethical, and psychosocial problems in the field of pediatrics) according to national regulations. A copy of the IRB/IEC-approved assent/consent form and documentation of approval must be provided to sponsor before initiation of the study.

In relation with the population of patients exposed in the trial, ie, pediatric/minor patients, the IRB/IEC should ensure proper advice from specialists with pediatrics expertise (competent in the area of clinical, ethical, and psychosocial problems in the field of pediatrics) according to national regulations.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients and their parents or legal guardian(s) must be informed of the new information and provide their written assent (if applicable) or consent if they wish the patient to continue in the study. The original signed revised assent/consent form must be maintained in the patient's study record and a copy must be given to the patient's parent(s) or legal guardian(s). If the race/ethnic origin of the patients will be collected in the clinical trial, the scientific justification should be specified in Section 14.5.

A locally approved specific consent form will be signed by patients who require Gilbert syndrome genetic testing (consent must be obtained prior to performing this assessment and local regulations should be respected).

12.3 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 IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, ICF, Investigator's Brochure, Investigator's curriculum vitae, etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

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

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the 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 IRB/IEC.

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

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

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

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The ICF 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 CRFs (eg, patient's medical file, appointment books, original laboratory records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

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

It is the responsibility of the Investigator to maintain adequate and accurate 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 in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

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 when available in the e-CRF 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.

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

13.5 USE OF COMPUTERIZED SYSTEMS

Computerized systems anticipated for use during the different steps of the study are listed below. New computerized systems may be established and the obsolete system may be deleted:

- For Screening and inclusion activities, IVRS/IWRS
- For data management activities, e-CRF (Rave Medidata)
- For statistical activities, SAS
- For pharmacovigilance activities, AWARE
- For monitoring activities, IMPACT
- For medical writing activities, Vault RIM.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-investigator will be signed, dated, and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

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

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

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

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

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

14.3 CONFIDENTIALITY

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

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

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

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

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

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

Subject race or ethnicity will be collected in this study because these data are required by several regulatory authorities (eg, on African-American population for FDA). Also, race/ethnicity data will be used as covariates in PopPK analysis as described in Section 11.4.5.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any

obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

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

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

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

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

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

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

14.8.1 By the Sponsor

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

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

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

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

14.8.2 By the Investigator

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

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

14.9 CLINICAL TRIAL RESULTS

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

14.10 PUBLICATIONS AND COMMUNICATIONS

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

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

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

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

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

The Investigator should not implement any deviation from, or changes 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 IRB/IEC prior to its implementation, unless there are overriding safety reasons.

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

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17 APPENDICES

Appendix A Subclassification of rheumatoid factor (RF)-negative, rheumatoid factor (RF)-positive polyarticular and oligoarticular juvenile idiopathic arthritis (JIA)

JIA subtypes	Clinical features defined by ILAR Classification	Exclusion criteria (footnote a)	Frequency (% of total JIA)*	Onset (yrs) Mean-range	Outcome
RF-negative pcJIA (5,7,6)	- Affects 5 or more joints in the first 6 months of disease. - Tests for RF negative - Tendosynovitis, uveitis, vasculitis	a, b, c, d, e	15%	7-9 yrs Two peaks: - early: 1-3 yrs - later: 6-12 yrs	- 10% destructive joint disease
RF-positive pcJIA (5) ANA	- ILAR Affects oJIA5 pcJIA or more joints in the first 6 months of disease. - Tests for RFpositive twice at least 2 months apart - Tenosynovitis, rheumatoid nodules, vasculitis, Sjögren's syndrome	a, b, c, e	5%	12-14 yrs 10 - 18 yrs	- Like adult RA - Seen in late childhood - Severe destructive joint disease
oJIA (5,7,6) • Persistent • Extended	- Affects no more than 4 joints throughout the disease course - Affects more than 4 joints after the first 6 months	a, b, c, d, e	50%	2-3 yrs 1-5 yrs	- Young age onset - Chronic uveitis, especially ANA+ - Leg length discrepancy - Destructive joint disease - Therapy as for pcJIA

a. Psoriasis or history of psoriasis in patients or first-degree relatives.
b. Arthritis in HLA B27 positive males beginning after the age of 6 years;
c. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, acute anterior uveitis, or history of 1 of these disorders in first-degree relatives;
d. Presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart;
e. Presence of systemic JIA in patients.

Appendix B Volume to be administered at each injection according to body weight

Notes:

1) Volume to be administrated at each injection during 12-week core treatment phase will be calculated based on Baseline (Visit 2) body weight and will be maintained during all 12-week core treatment phase.

2) Volume to be administrated during the extension treatment phase will be adjustable by body weight measured at each visit in case of weight increase and if the calculation shows a need for dose increase.

3) If the selected dose regimen is one from the 3 predefined dose regimens, the patients subsequently enrolled at or changed to the selected dose regimen will use the corresponding dose in the tables below.

4) If the selected dose regimen is an intermediate dose, corresponding tables will be provided to the Investigators.

B.1 Patient in high weight group (Group A): Patients ≥30 kg and ≤60 kg for dose-finding portion and ≥30 kg for additional patients in the second portion

- Dose Regimen 1 and 3 Cohorts

Dose Regimen 1 Cohort (2 mg/kg q2w) and Dose Regimen 3 Cohort (2 mg/kg qw)		
Body weight (kg)	**Volume per injection (mL)**	**Corresponding dose (mg)**
≥30 and <33	0.35	61.25
≥33 and <37.5	0.40	70
≥37.5 and <42	0.45	78.75
≥42 and <46.5	0.50	87.5
≥46.5 and <50.5	0.55	96.25
≥50.5 and <55	0.60	105
≥55 and <59.5	0.65	113.75
≥59.5 and <64	0.70	122.5
≥64 and <68	0.75	131.25
≥68 and <72.5	0.80	140
≥72.5	0.85 (cap injection volume)	148.75 (cap under 150 mg)

- Dose Regimen 2 Cohort

Dose Regimen 2 Cohort (3 mg/kg q2w)		
Body weight (kg)	**Volume per injection (mL)**	**Corresponding dose (mg)**
≥30 and <31	0.50	87.5
≥31 and <34	0.55	96.25
≥34 and <37	0.60	105
≥37 and <39.5	0.65	113.75
≥39.5 and <42.5	0.70	122.5
≥42.5 and <45	0.75	131.25
≥45 and <48.5	0.80	140
≥48.5 and <51.5	0.85	148.75
≥51.5 and <54.5	0.90	157.5
≥54.5 and <57	0.95	166.25
≥57 and <63	1.00	175
≥63	1.1 (cap injection volume)	192.5 (cap under 200 mg)

B.2 Patient in low weight group (Group B): <30 kg and ≥10 kg

- Dose Regimens 1 and 3 Cohorts

Dose Regimen 1 Cohort (2.5 mg/kg q2w) and Dose Regimen 3 Cohort (2.5 mg/kg qw)		
Body weight (kg)	**Volume per injection (mL)**	**Corresponding dose (mg)**
≥10 and <12.5	0.15	26.25
≥12.5 and <16	0.20	35
≥16 and <19.5	0.25	43.75
≥19.5 and <23	0.30	52.5
≥23 and <26.5	0.35	61.25
≥26.5 and <30	0.40	70
For patients who grow over 30 kg, the following injection volume will be followed		
≥30 and <37.5	0.40	70
≥37.5 and <42	0.45	78.75
≥42 and <46.5	0.50	87.5
≥46.5 and <50.5	0.55	96.25
≥50.5 and <55	0.60	105
≥55 and <59.5	0.65	113.75
≥59.5 and <64	0.70	122.5
≥64 and <68	0.75	131.25
≥68 and <72.5	0.80	140
≥72.5	0.85 (cap injection volume)	148.75 (cap under 150 mg)

- Dose Regimen 2 Cohort

Dose Regimen 2 Cohort (4 mg/kg q2w)		
Body weight (kg)	**Volume per injection (mL)**	**Corresponding dose (mg)**
≥10 and <12.5	0.25	43.75
≥12.5 and <14.5	0.30	52.5
≥14.5 and <16.5	0.35	61.25
≥16.5 and <19	0.40	70
≥19 and <21	0.45	78.75
≥21 and <23.5	0.50	87.5
≥23.5 and <25.5	0.55	96.25
≥25.5 and <27.5	0.60	105
≥27.5 and <30	0.65	113.75
For patients who grow over 30 kg, the following injection volume will be followed		
≥30 and <39.5	0.65	113.75
≥39.5 and <42.5	0.70	122.5
≥42.5 and <45	0.75	131.25
≥45 and <48.5	0.80	140
≥48.5 and <51.5	0.85	148.75
≥51.5 and <54.5	0.90	157.5
≥54.5 and <57	0.95	166.25
≥57 and <60.5	1.00	175
≥60.5 and <63	1.00	175
≥63	1.1 (cap injection volume)	192.5 (cap under 200 mg)

Appendix C Definition of Efficacy and JIA ACR 30/50/70/90/100

In the dose-finding and second portions, patients who do not achieve a JIA ACR30 by the end of the 12-week core treatment phase should be discontinued from the study treatment to receive standard of care as per the Investigator's clinical judgment. Assessment for lack of efficacy may be initiated after the patient has received at least six weeks of study treatments.

The definition for improvement in JIA [ACR Pediatric 30 criteria (Pedi30)] defines ≥3/6 core set variables improved ≥30% from baseline with no more than 1/6 worsened by ≥30% (3, 22)

The definition for improvement in JIA [ACR Pediatric 50 criteria (Pedi50)] defines ≥3/6 core set variables improved ≥50% from baseline with no more than 1/6 worsened by ≥30%

The definition for improvement in JIA [ACR Pediatric 70 criteria (Pedi70)] defines ≥3/6 core set variables improved ≥70% from baseline with no more than 1/6 worsened by ≥30%

The definition for improvement in JIA [ACR Pediatric 90 criteria (Pedi90)] defines ≥3/6 core set variables improved at least 90% from baseline with no more than 1/6 worsened by ≥30%

The definition for improvement in JIA [ACR Pediatric 100 criteria (Pedi100)] defines ≥3/6 core set variables improved ≥100% from baseline with no more than 1/6 worsened by ≥30%

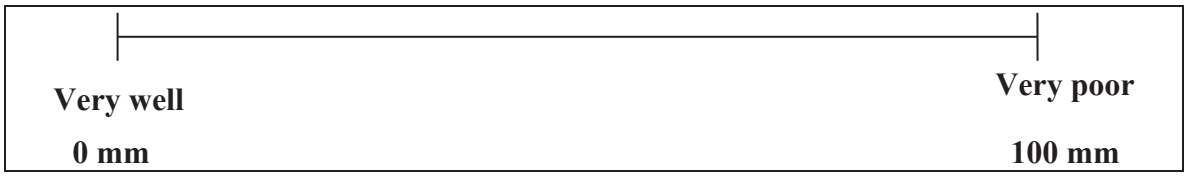
ACR JIA Core Set Includes:

- Physician global assessment of disease activity - Visual Analogue Scale (VAS)
- Parent or patient assessment of overall well-being
- Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI)
- Number of joints with active arthritis
- Number of joints with limited range of motion
- Index of inflammation: hs-CRP.

Appendix D Subject's and Physician's Global Assessment of Disease Activity

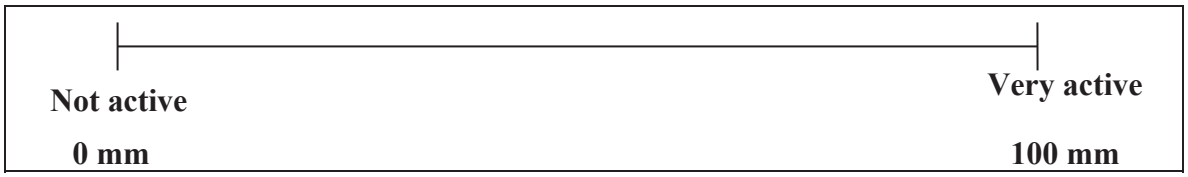
SUBJECT'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY

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



PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY

Place a vertical mark on the line rating your patient's current activity level



Appendix E Childhood Health Assessment Questionnaire

CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE

In this section we are interested in learning how your child's illness affects his/her ability to function in daily life. Please feel free to add any comments on the back of this page. In the following questions, please check the one response which best describes your child's usual activities (averaged over an entire day) **OVER THE PAST WEEK. ONLY NOTE THOSE DIFFICULTIES OR LIMITATIONS WHICH ARE DUE TO ILLNESS.** If most children at your child's age are not expected to do a certain activity, please mark it as "Not Applicable". **For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young but not because he/she is RESTRICTED BY ILLNESS, please mark it as "NOT Applicable".**

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicable
DRESSING & GROOMING					
Is your child able to:					
- Dress, including tying shoelaces and doing buttons?	☐	☐	☐	☐	☐
- Shampoo his/her hair?	☐	☐	☐	☐	☐
- Remove socks?	☐	☐	☐	☐	☐
- Cut fingernails?	☐	☐	☐	☐	☐
ARISING					
Is your child able to:					
- Stand up from a low chair or floor?	☐	☐	☐	☐	☐
- Get in and out of bed or stand up in a crib?	☐	☐	☐	☐	☐
EATING					
Is your child able to:					
- Cut his/her own meat?	☐	☐	☐	☐	☐
- Lift up a cup or glass to mouth?	☐	☐	☐	☐	☐
- Open a new cereal box?	☐	☐	☐	☐	☐
WALKING					
Is your child able to:					
- Walk outdoors on flat ground?	☐	☐	☐	☐	☐
- Climb up five steps?	☐	☐	☐	☐	☐

*** Please check any AIDS or DEVICES that your child usually uses for any of the above activities:**

- Cane	☐	- Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)	☐
- Walker	☐	- Built up pencil or special utensils	☐
- Crutches	☐	- Special or built up chair	☐
- Wheelchair	☐	- Other (Specify:_____)	☐

*** Please check any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

- Dressing and Grooming	☐	- Eating	☐
- Arising	☐	- Walking	☐

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicable
HYGIENE					
Is your child able to:					
- Wash and dry entire body?	☐	☐	☐	☐	☐
- Take a tub bath (get in and out of tub)?	☐	☐	☐	☐	☐
- Get on and off the toilet or potty chair?	☐	☐	☐	☐	☐
- Brush teeth?	☐	☐	☐	☐	☐
- Comb/brush hair?	☐	☐	☐	☐	☐
REACH					
Is your child able to:					
- Reach and get down a heavy object such as a large game or books from just above his/her head?	☐	☐	☐	☐	☐
- Bend down to pick up clothing or a piece of paper from the floor?	☐	☐	☐	☐	☐
- Pull on a sweater over his/her head?	☐	☐	☐	☐	☐
- Turn neck to look back over shoulder?	☐	☐	☐	☐	☐
GRIP					
Is your child able to:					
- Write or scribble with pen or pencil?	☐	☐	☐	☐	☐
- Open car doors?	☐	☐	☐	☐	☐
- Open jars which have been previously opened?	☐	☐	☐	☐	☐
- Turn faucets on and off?	☐	☐	☐	☐	☐
- Push open a door when he/she has to turn a door knob?	☐	☐	☐	☐	☐
ACTIVITIES					
Is your child able to:					
- Run errands and shop?	☐	☐	☐	☐	☐
- Get in and out of a car or toy car or school bus?	☐	☐	☐	☐	☐
- Ride bike or tricycle?	☐	☐	☐	☐	☐
- Do household chores (e.g. wash dishes, take out trash, vacuuming, yardwork, make bed, clean room)?	☐	☐	☐	☐	☐
- Run and play?	☐	☐	☐	☐	☐

*** Please check any AIDS or DEVICES that your child usually uses for any of the above activities:**

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

*** Please check any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

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

PAIN: We are also interested in learning whether or not your child has been affected by pain because of his or her illness. How much pain do you think your child has had because of his/her illness IN THE PAST WEEK? Place a mark on the line below, to indicate the severity of the pain

No pain 0 ├──────────────────────────────────────┤ 100 Very severe pain

GLOBAL EVALUATION: Considering all the ways that arthritis affects your child, rate how he/she is doing by placing a single mark on the line below.

Very well 0 ├──────────────────────────────────────┤ 100 Very poor

Appendix F Tanner Stages

Tanner Stage	Female				Male				
	Age range (years)	Breast growth	Pubic hair growth	Other changes	Age range (years)	Testes growth	Penis growth	Pubic hair growth	Other changes
I	0–15	Pre-adolescent	None	Pre-adolescent	0–15	Pre-adolescent testes (≤2.5 cm)	Pre-adolescent	None	Pre-adolescent
II	8–15	Breast budding (thelarche); areolar hyperplasia with small amount of breast tissue	Long downy pubic hair near the labia, often appearing with breast budding or several weeks or months later	Peak growth velocity often occurs soon after stage II	10–15	Enlargement of testes; pigmentation of scrotal sac	Minimal or no enlargement	Long downy hair, often appearing several months after testicular growth; variable pattern noted with pubarche	Not applicable
III	10–15	Further enlargement of breast tissue and areola, with no separation of their contours	Increase in amount and pigmentation of hair	Menarche occurs in 2% of girls late in stage III	1½–16.5	Further enlargement	Significant enlargement, especially in diameter	Increase in amount; curling	Not applicable
IV	10–17	Separation of contours; areola and nipple form secondary mound above breasts tissue	Adult in type but not in distribution	Menarche occurs in most girls in stage IV, 1–3 years after thelarche	Variable: 12–17	Further enlargement	Further enlargement, especially in diameter	Adult in type but not in distribution	Development of axillary hair and some facial hair
V	12.5–18	Large breast with single contour	Adult in distribution	Menarche occurs in 10% of girls in stage V.	13–18	Adult in size	Adult in size	Adult in distribution (medial aspects of thighs; linea alba)	Body hair continues to grow and muscles continue to increase in size for several months to years; 20% of boys reach peak growth velocity during this period

The Tanner stage is a scale of physical development in children, adolescents and adults. The scale defines physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breast, genitals, testicular volume and development of pubic hair. This scale was first identified by James Tanner, a British pediatrician.

Reference:

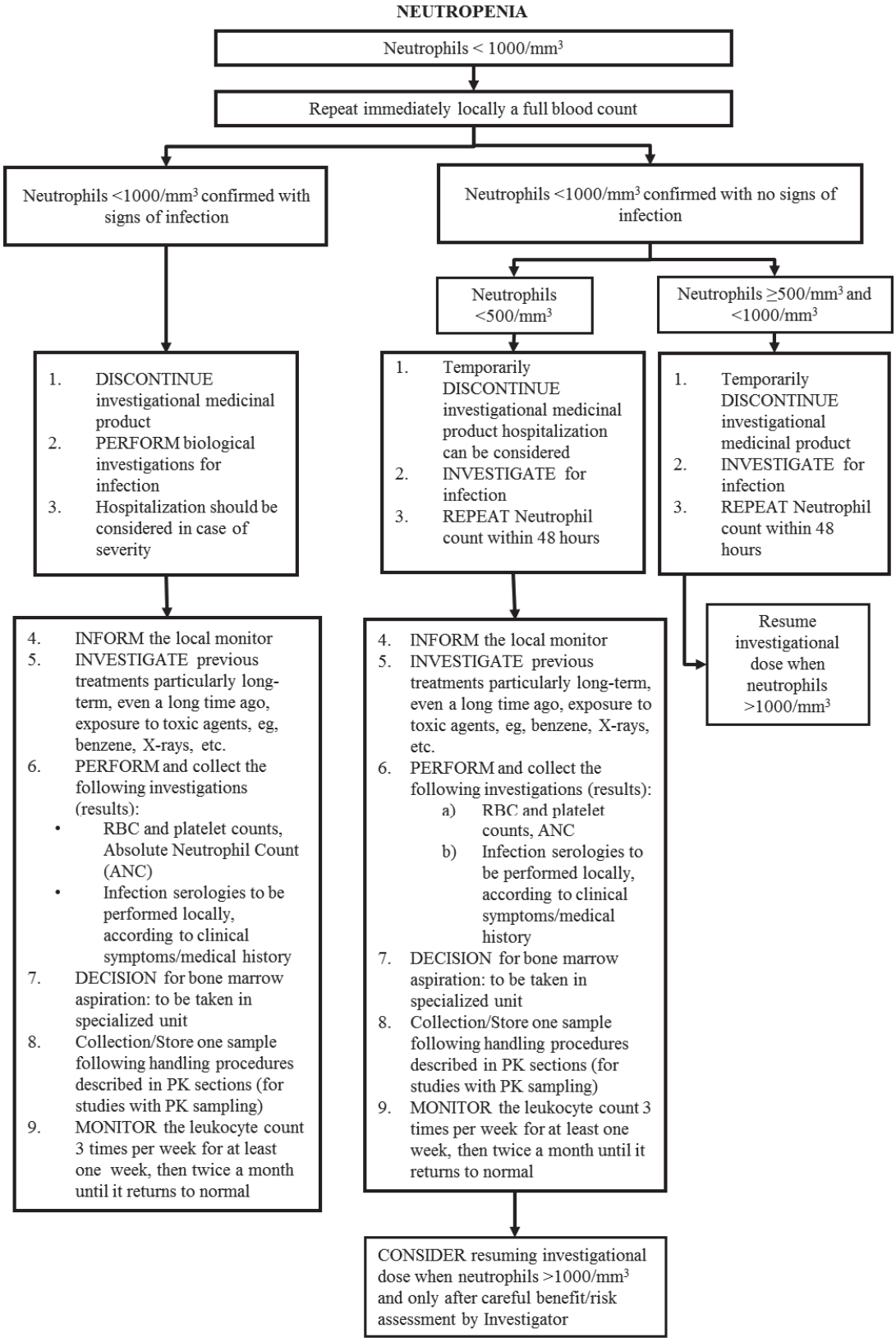
Marshall WA, Tanner JM (February 1970). "Variations in the pattern of pubertal changes in boys". Arch. Dis. Child. 45 (239): 13–23. doi:10.1136/adc.45.239.13. PMC 2020414. PMID 5440182.

Marshall WA, Tanner JM (June 1969). "Variations in pattern of pubertal changes in girls". Arch. Dis. Child. 44 (235): 291–303. doi:10.1136/adc.44.235.291. PMC 2020314. PMID 5785179.

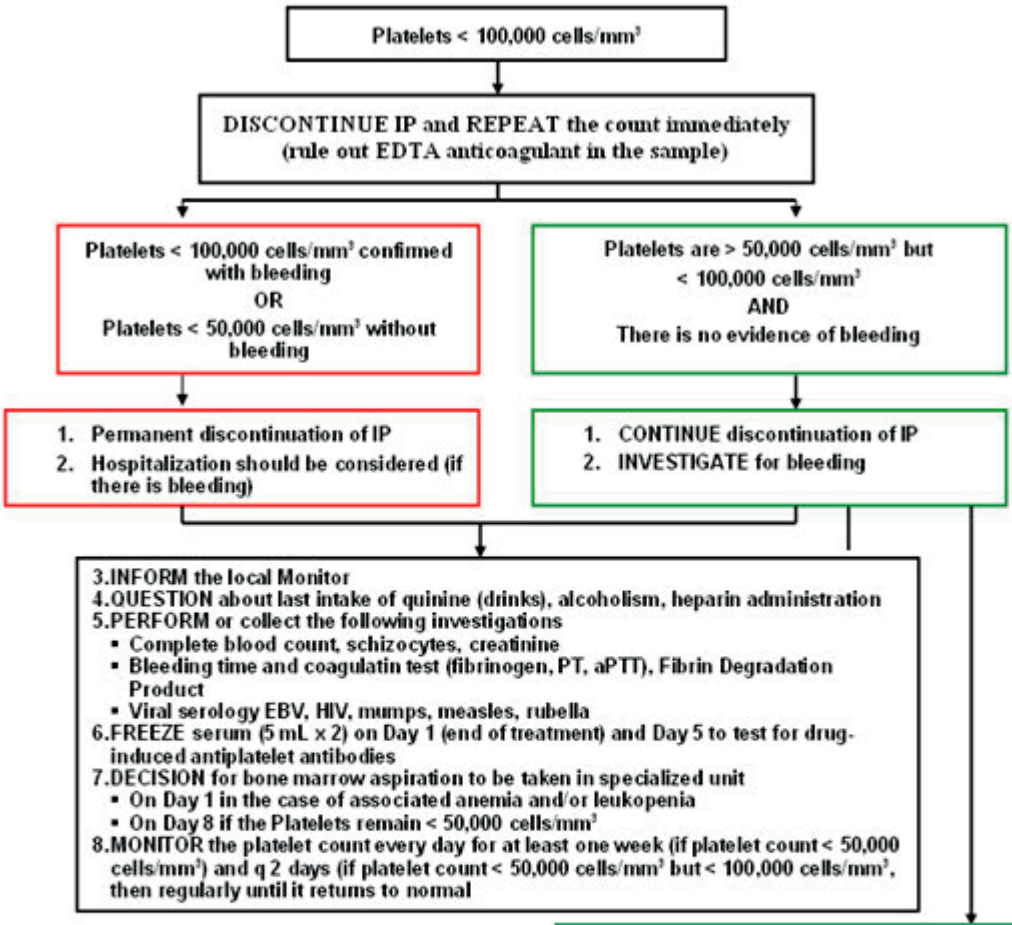
Encyclopedia of Children's Health; Puberty: w.healthofchildren.com/P/Puberty.html

Source: http://www.ncbi.nlm.nih.gov/books/NBK138588/table/annexh.t1/?report=objectonly

Appendix G General Guidance for the follow-up of laboratory abnormalities by Sanofi



Thrombocytopenia



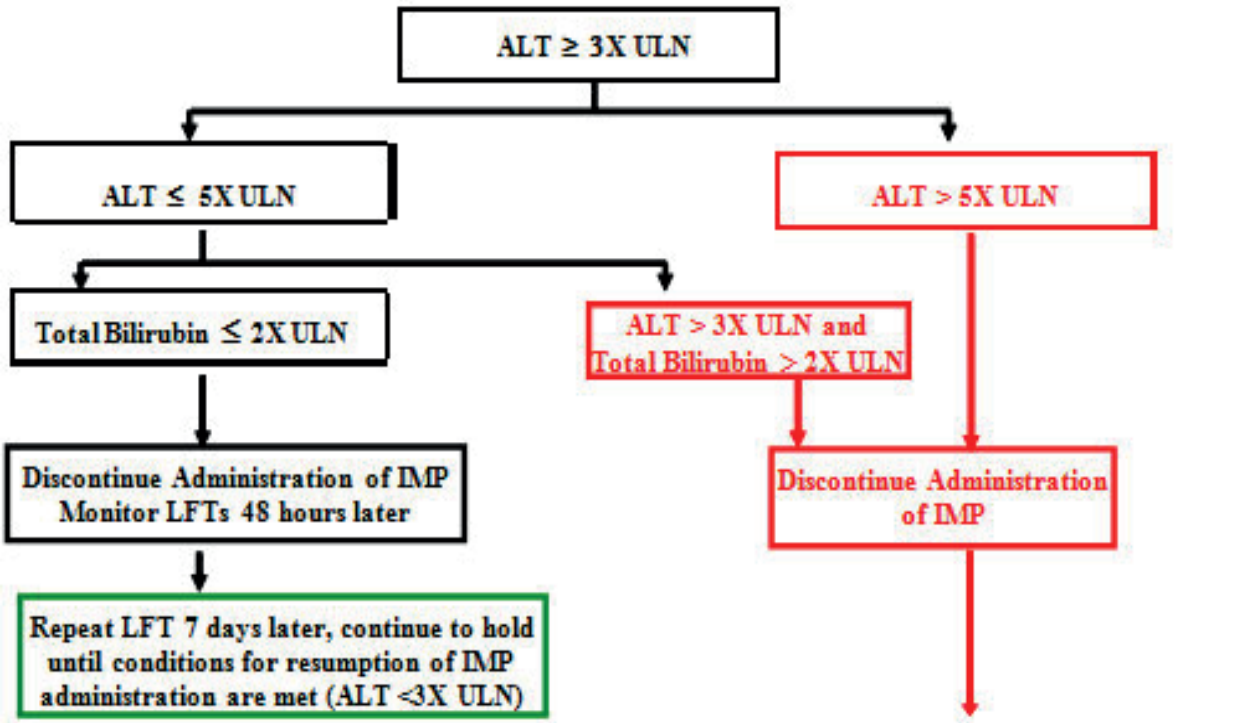
Note: the procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (eg, for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as an AE only if it is

- Symptomatic, and/or
- Requiring either corrective treatment or consultation, and/or

If platelet count returns to > 100,000 cells/mm³, investigational medicinal product may be resumed at the discretion of the Investigator.

INCREASE IN ALT

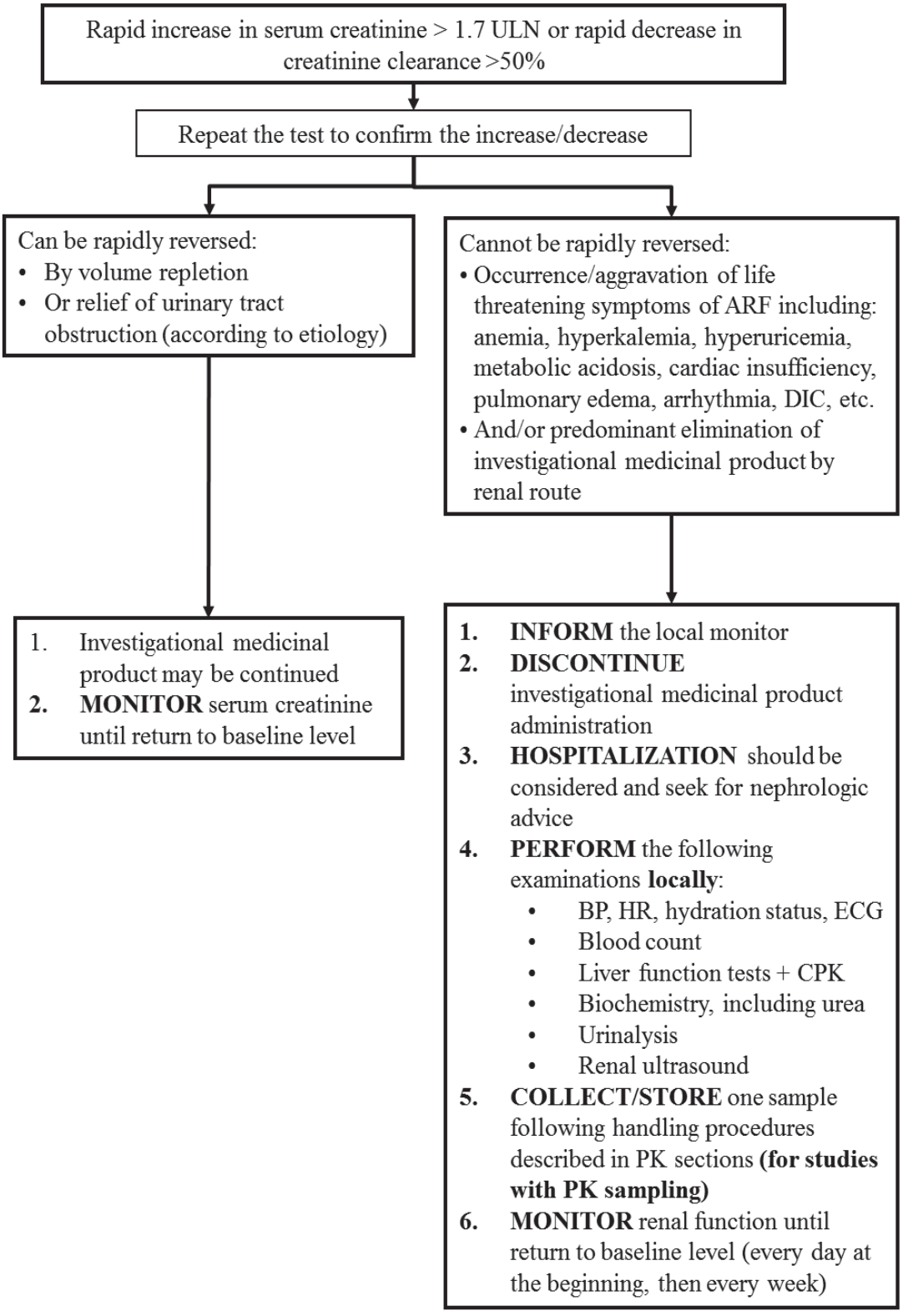


In ANY CASE, **FOLLOW** the instructions #1 to #8 listed in the box below.

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

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

INCREASE IN SERUM CREATININE IN PATIENTS WITH NORMAL BASELINE



Appendix H Anaphylaxis definition

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

(Adapted from Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117: 391-7)

Clinical criteria for diagnosing anaphylaxis

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

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

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

Appendix I List of opportunistic infections

- Aspergillosis
- Blastomyces dermatitidis (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.

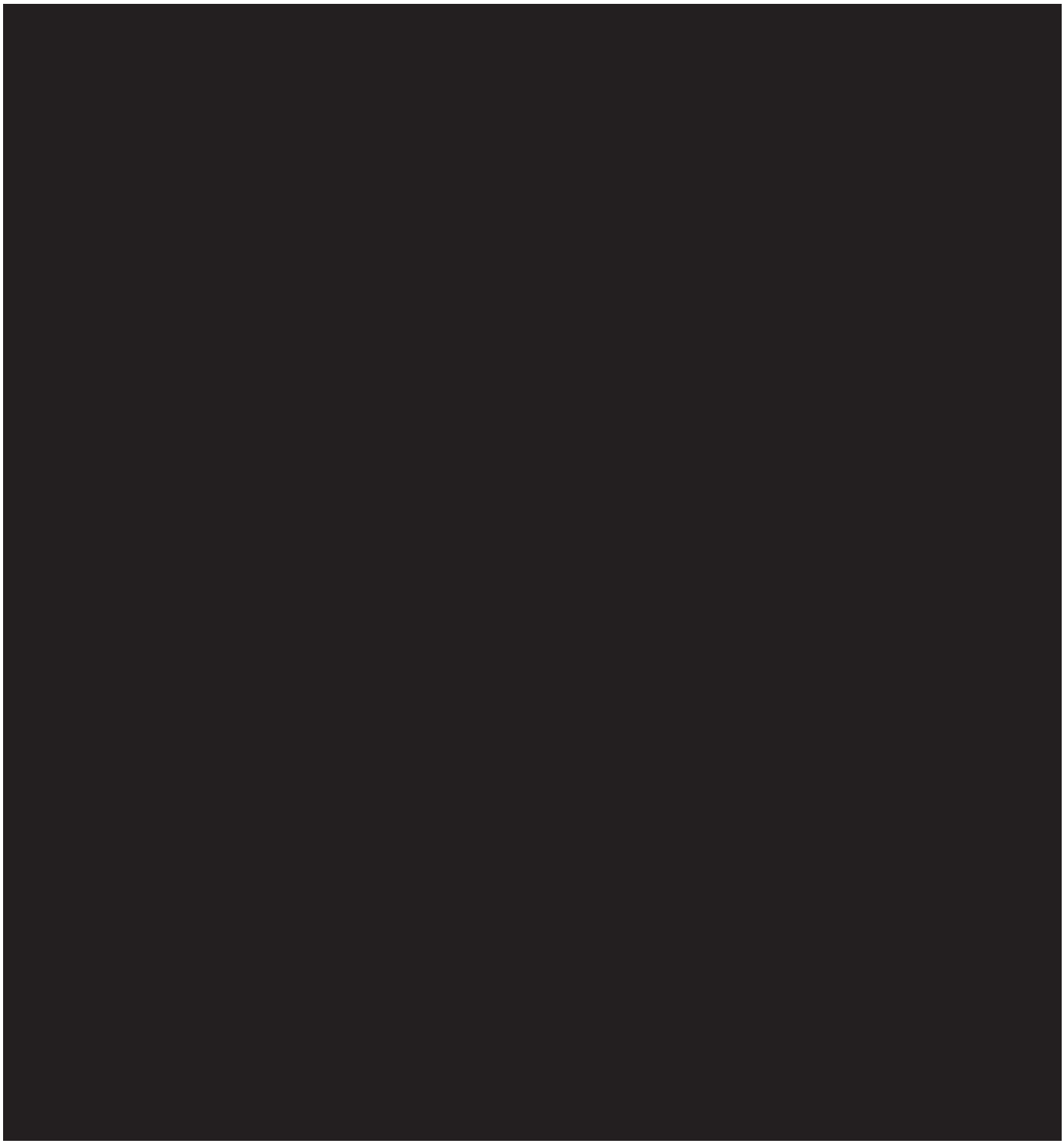
Appendix J Prohibited live (attenuated) vaccine list

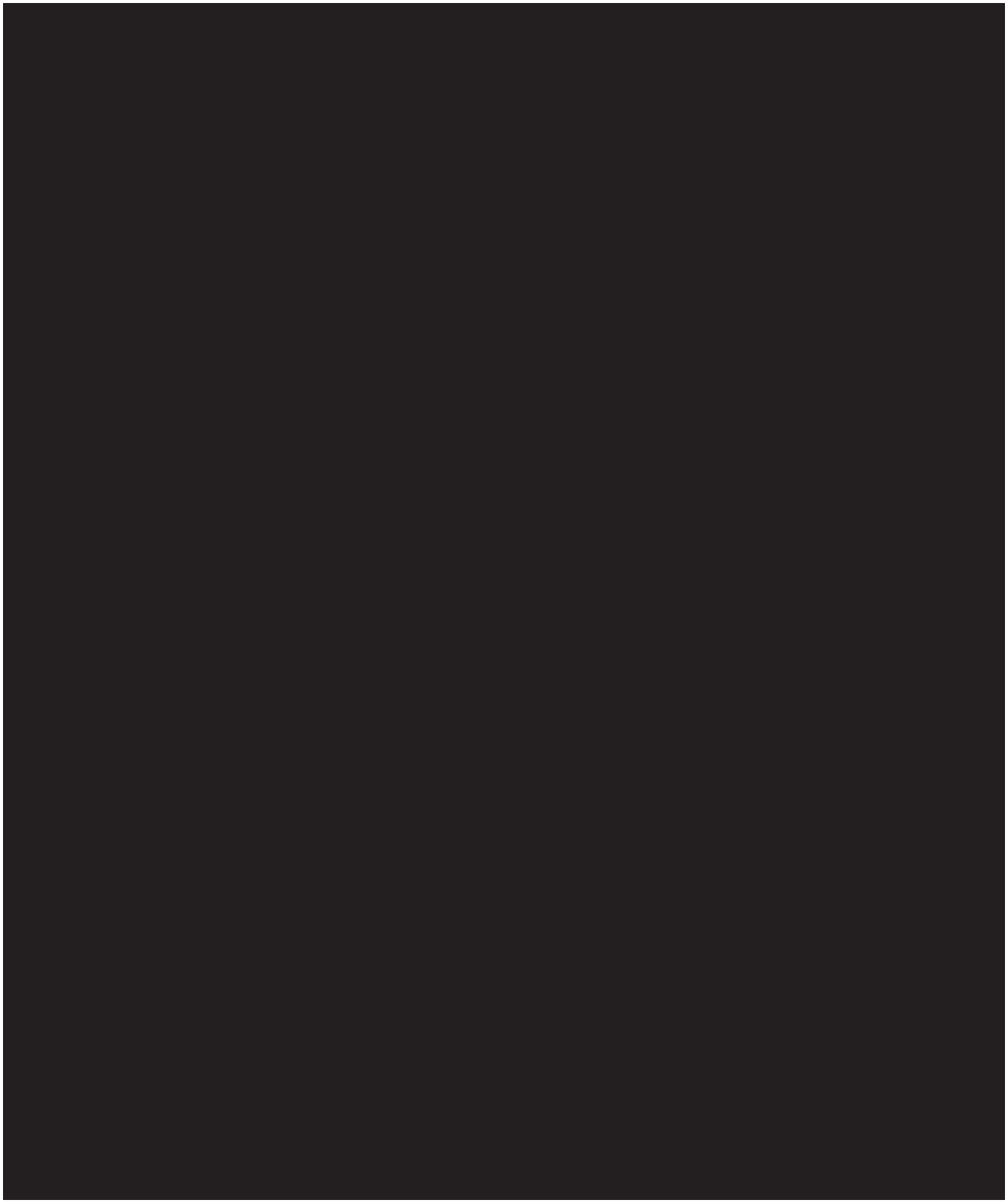
Chickenpox (Varicella)
Intranasal influenza
Measles (Rubeola)
Measles-mumps-rubella (MMR) combination
Mumps
Oral polio (Sabin)
Oral typhoid
Rubella
Smallpox (Vaccinia)
Shingles (Herpes zoster)
Bacille Calmette-Guerin
Yellow fever

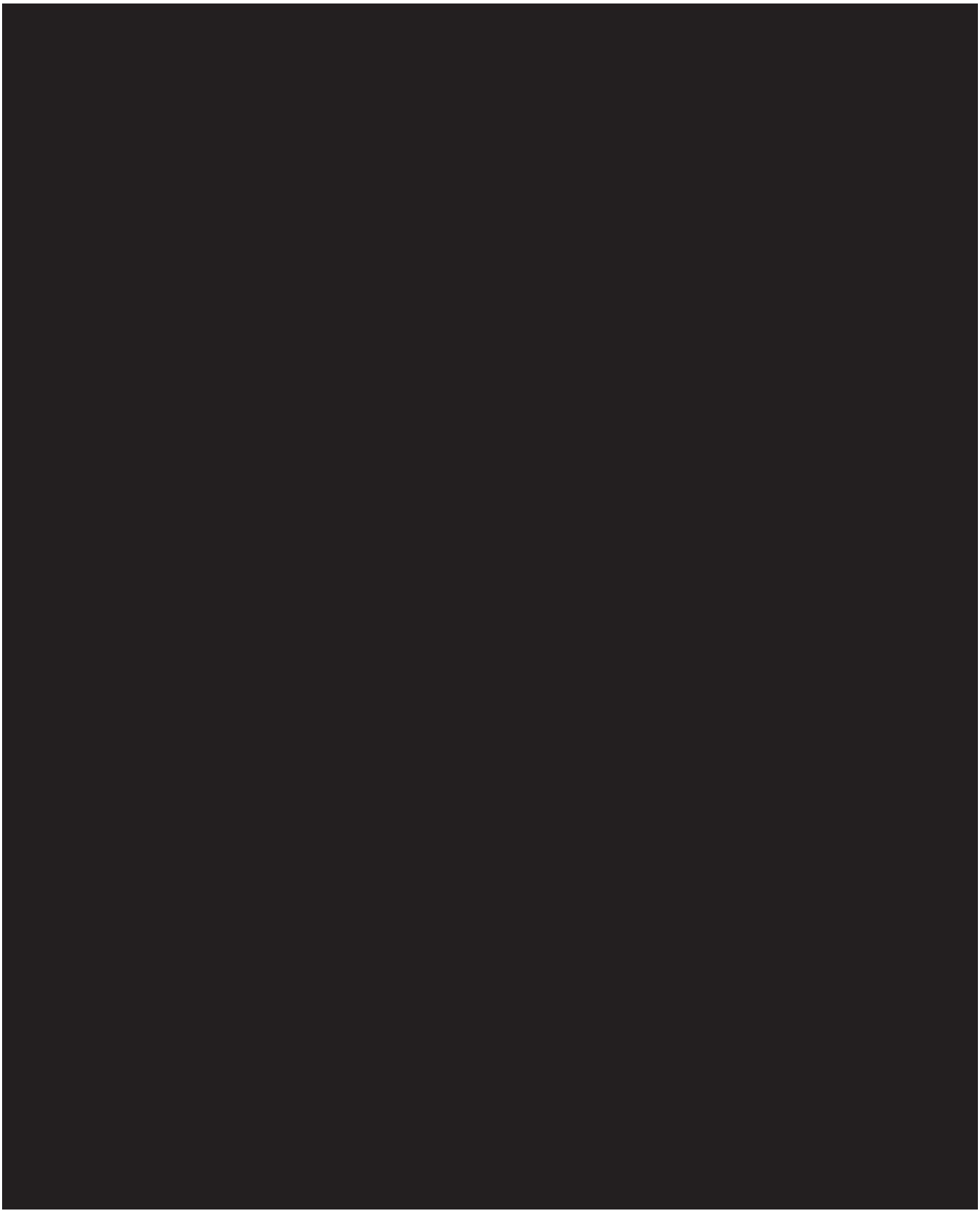
Note: This list is indicative and not exhaustive.

Appendix K Country specific requirements

Country specific requirements are included in the body of the protocol.







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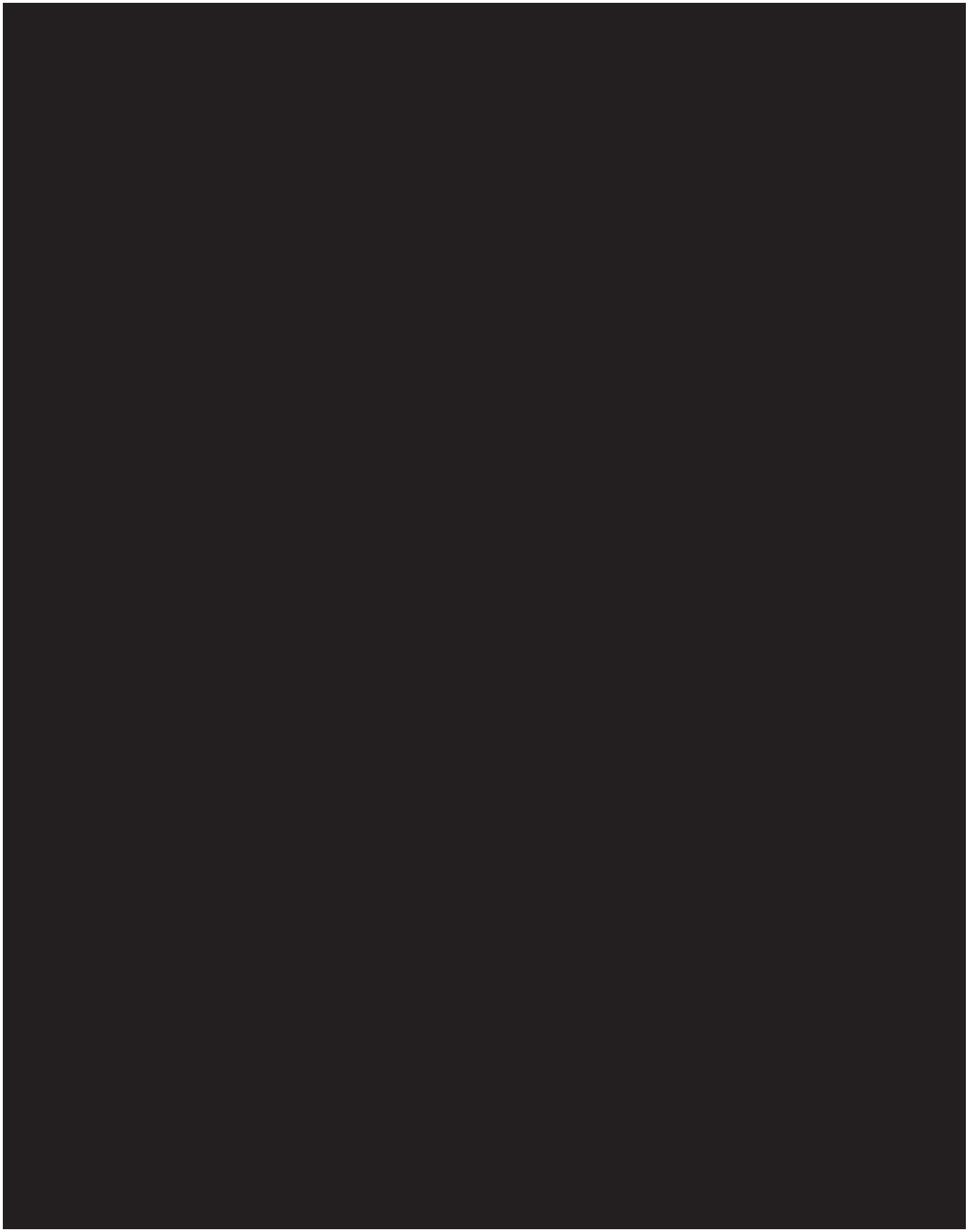

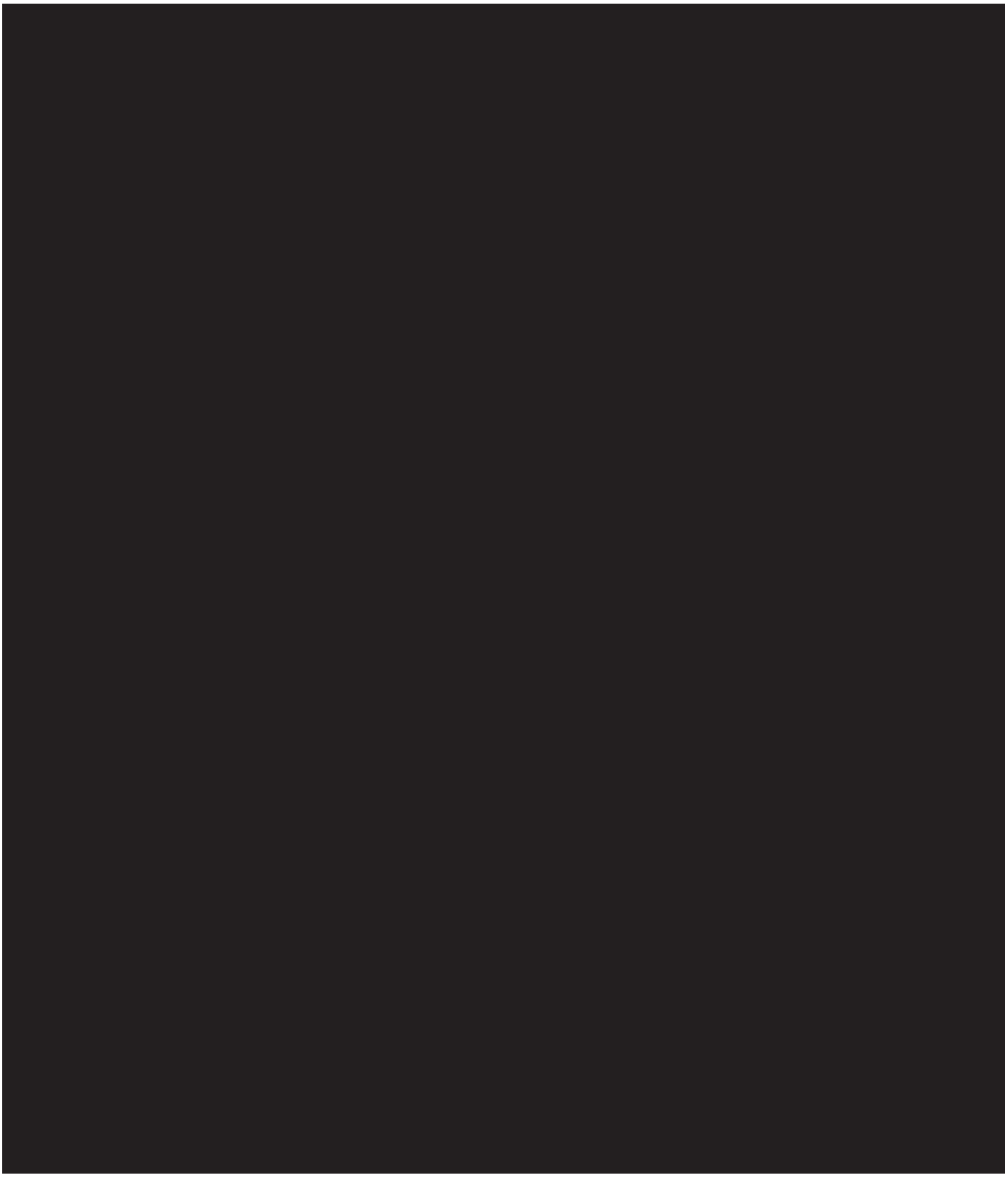

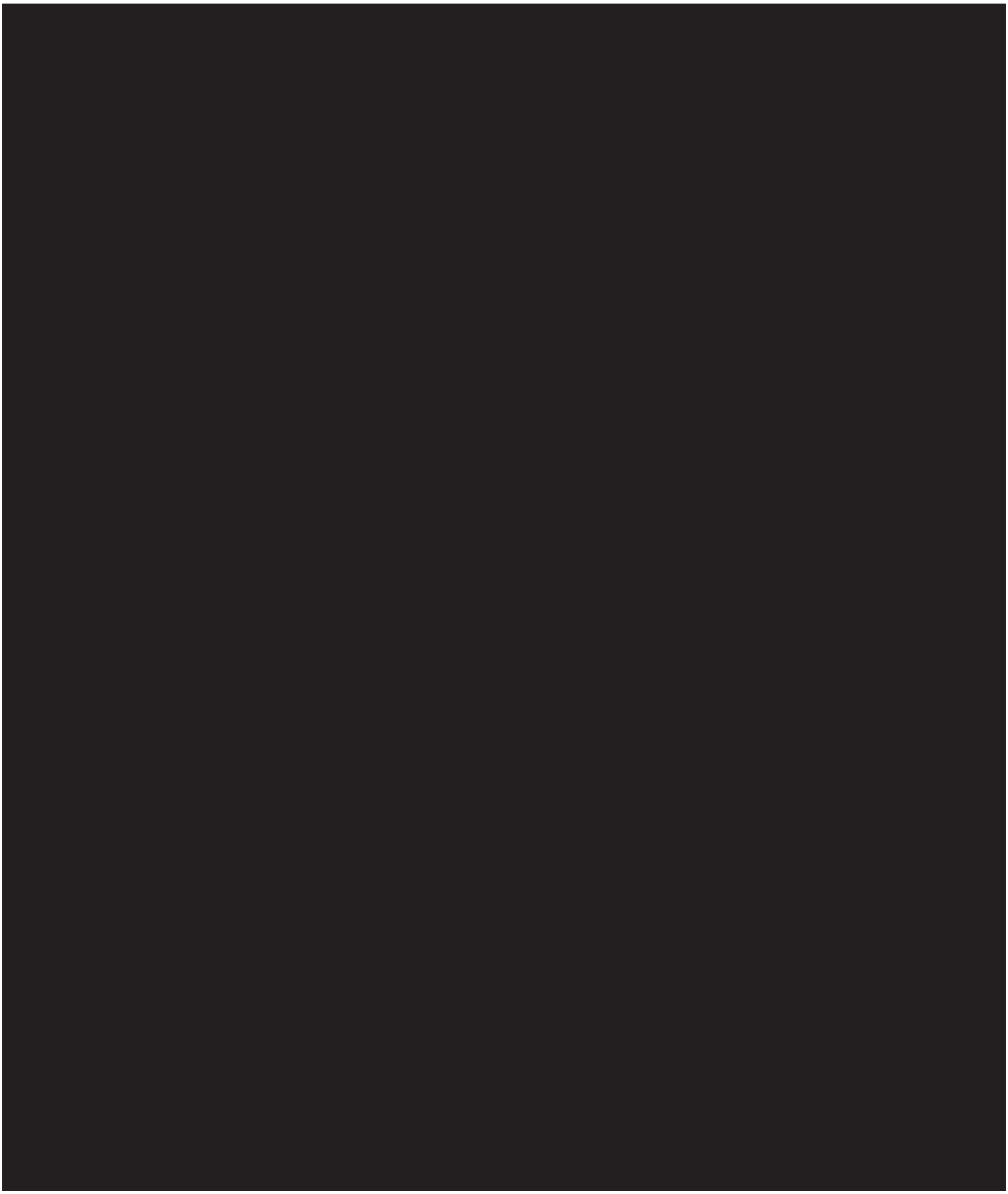

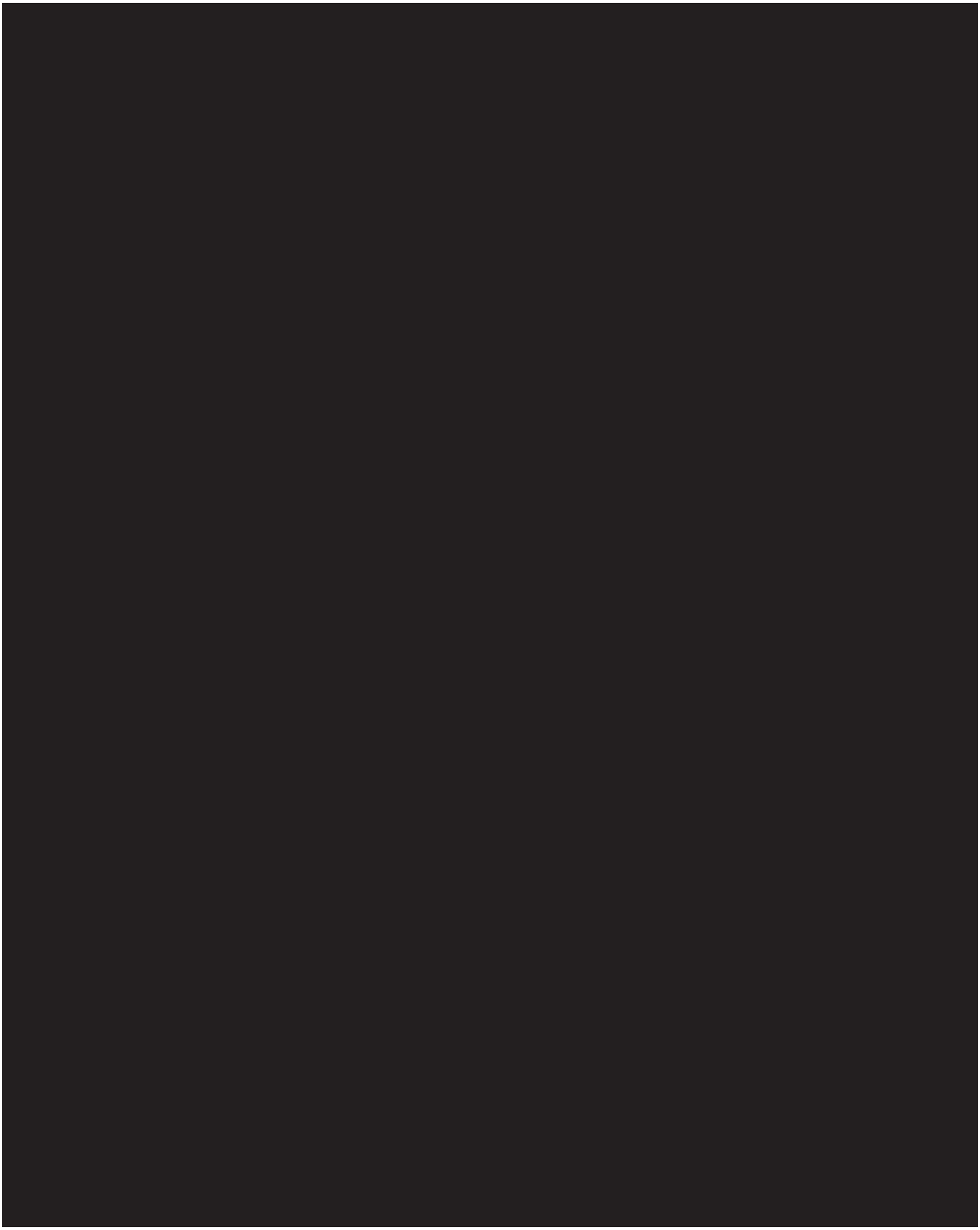

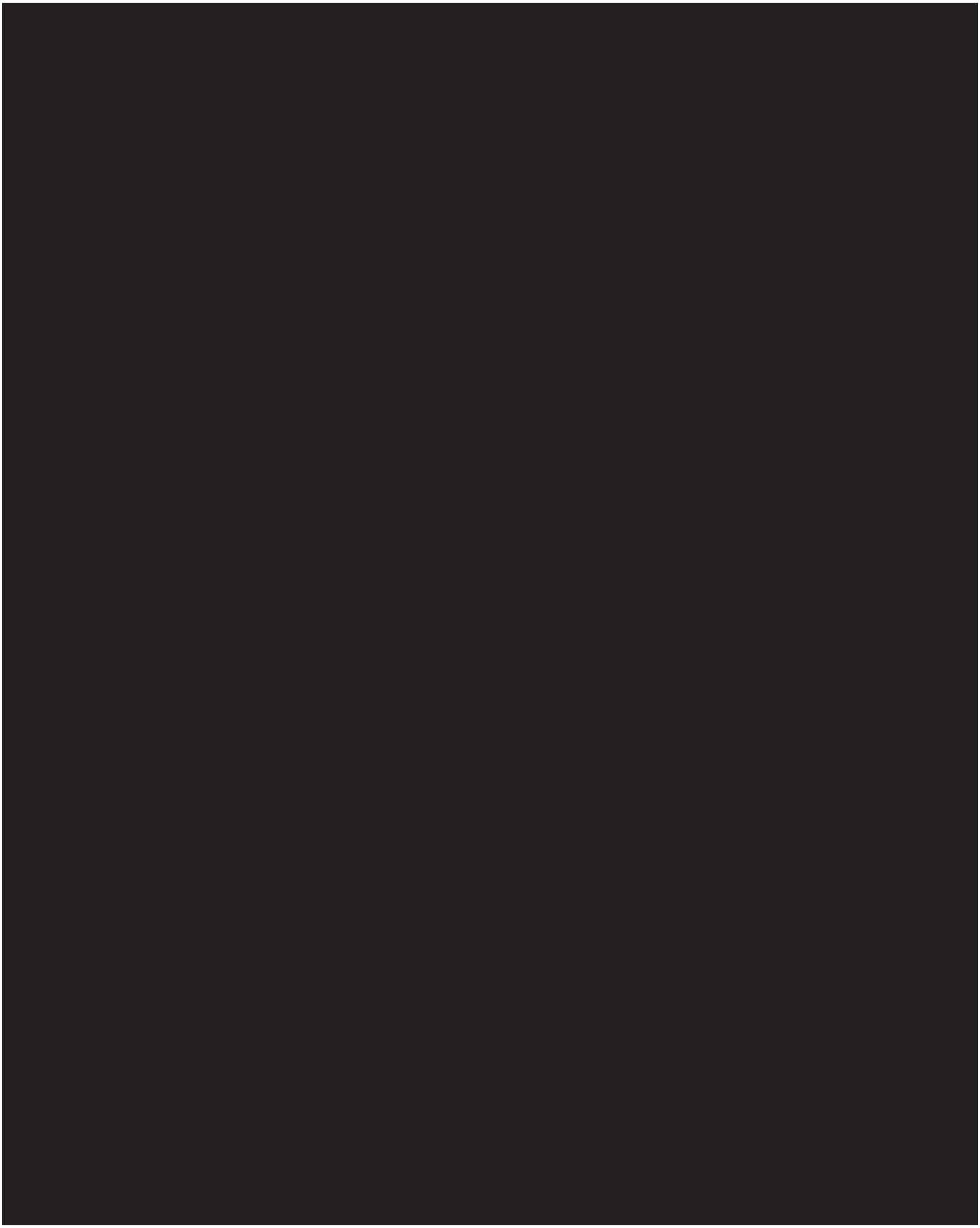

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