NCT02776735

STATISTICAL ANALYSIS PLAN

Open-label, Sequential, Ascending, Repeated Dose-finding Studies of Sarilumab, Administered with Subcutaneous (SC) Injection, in Children and Adolescents, Either Aged 2 to 17 Years with Polyarticular-course Juvenile Idiopathic Arthritis (pcJIA) or Aged 1 to 17 Years with Systemic Juvenile Idiopathic Arthritis (sJIA), Followed by an Extension Phase

SAR153191-DRI13925[redacted]

STUDY BIOSTATISTICIAN: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACR:	American College of Rheumatology
ADA:	antidrug antibody
AE:	adverse event(s)
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
AST:	aspartate aminotransferase
ATC:	anatomic therapeutic class
BMI:	body mass index
BUN:	blood urea nitrogen
CHAQ:	Childhood Health Assessment Questionnaire
CLcr:	creatinine clearance
CRF:	case report form
DBL:	database lock
DBP:	diastolic blood pressure
DEC:	Dose Escalation Committee
DMARDs:	disease-modifying antirheumatic drug(s)
DMC:	Data Monitoring Committee
EBV:	Epstein Barr Virus
EOS:	end of study
EOT:	end of treatment
HBc-Ab:	hepatitis B core antibody
HBs-Ab:	hepatitis B surface antibody
HBs-Ag:	hepatitis B surface antigen
HCV-Ab:	hepatitis C antibody
HDL:	high density lipoprotein
HLGT:	high-level group term
HLT:	high-level term
IMP:	investigational medicinal product
IVRS:	Interactive Voice Response System
IWRS:	Interactive Web Response System
JADAS-27:	Juvenile Arthritis Disease Activity Score-27
JIA:	juvenile idiopathic arthritis
LDH:	lactate dehydrogenase
LDL:	low density lipoprotein
LFT:	liver function test
LLN:	lower limit of normal
LLOQ:	lower limit of quantification
LLT:	lower-level term

MAS:	macrophage activating syndrome
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	modified intent-to-treat
MTX:	methotrexate
NSAIDs:	non-steroidal anti-inflammatory drug(s)
pcJIA:	polyarticular-course juvenile idiopathic arthritis
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PK:	pharmacokinetic
PopPK:	population pharmacokinetic
PT:	preferred term
q2w:	every 2 weeks
qw:	every week
RA:	rheumatoid arthritis
RBC:	red blood cell
SAE:	serious adverse event(s)
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SD:	standard deviation
SEM:	standard error of the mean
SGOT:	serum glutamic-oxaloacetic transaminase
SGPT:	serum glutamic-pyruvic transaminase
[redacted]	[redacted]
SOC:	system organ class
TEAE:	treatment-emergent adverse event
TG:	triglycerides
ULN:	upper limit of normal
VAS:	visual analogue scale
WBC:	white blood cell
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

This statistical analysis plan (SAP) provides a comprehensive and detailed description of statistical strategy and methodology to be used to analyze the data from the open-label, sequential, ascending, repeated dose-finding sarilumab/SAR153191 DRI13925 studies. the first experience of sarilumab in pediatrics and will be conducted ,

1.1 STUDY DESIGN AND RANDOMIZATION

are phase 2b, multicenter, worldwide, open-label, sequential, ascending, repeated dose-finding studies in two distinct weight groups (A: ≥30 kg; B: <30 kg) of patients aged 2 to 17 years with polyarticular-course juvenile idiopathic arthritis (pcJIA; DRI13925) Each study has 2 parts, a 12-week core treatment part and an extension.

The 3 sequential ascending doses planned to be tested

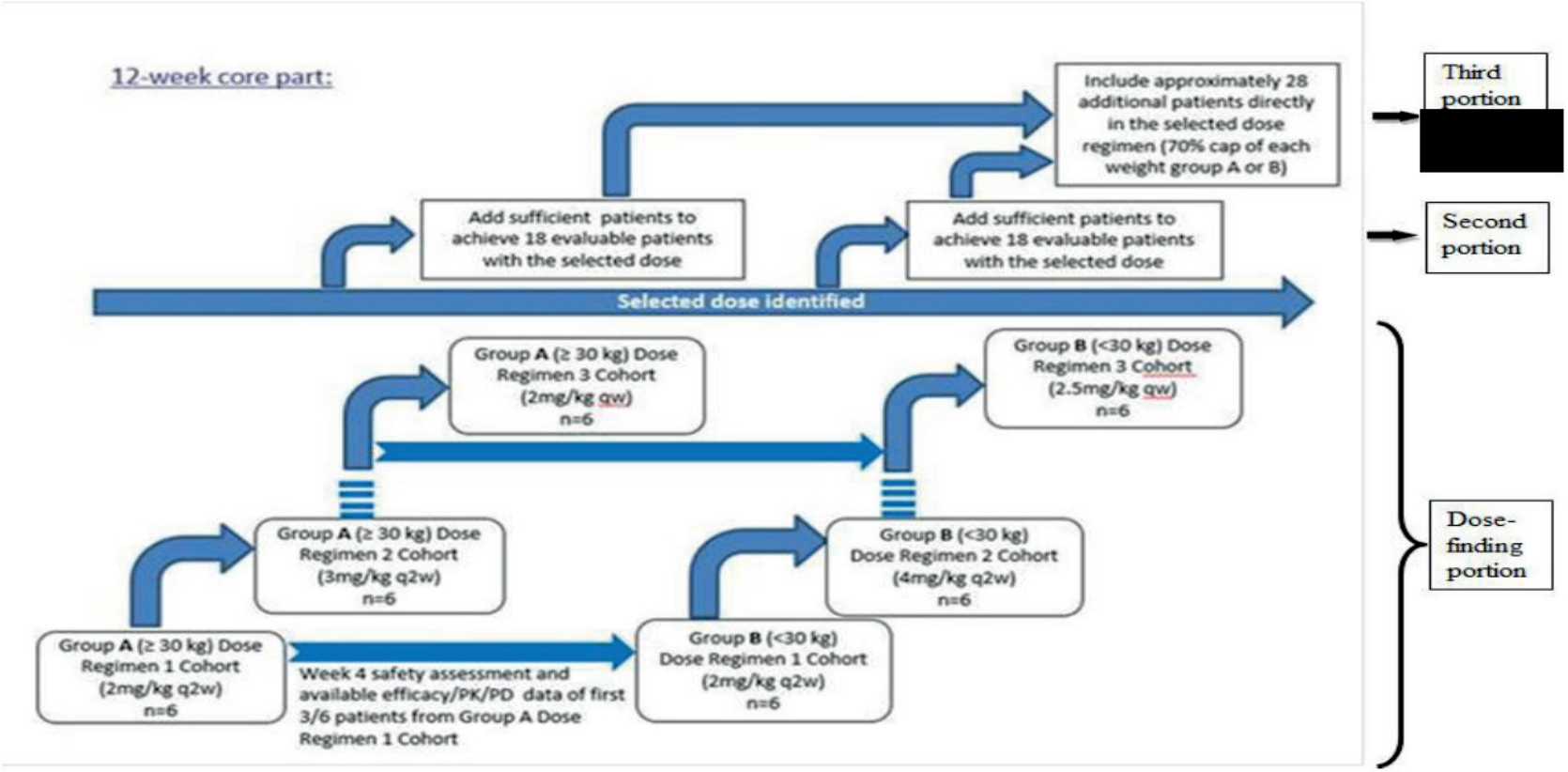
- Dose Regimen 1: dose targeting pharmacokinetic (PK) exposures similar to sarilumab 150 mg q2w, the lowest effective dose in adult patients with rheumatoid arthritis (RA)
- Dose Regimen 2: dose with targeted PK exposures similar to sarilumab 200 mg q2w in adult patients with RA
- Dose Regimen 3: dose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

Table 1 - Dose regimens for each weight group

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

The graphical presentation of the study design including the dose escalation, dose selection, and the 3 portions (the third portion is for pcJIA study only) during the 12-week core treatment part is provided in Figure 1.

Figure 1 - Study design - dose escalation, dose selection, and the 3 portions during the 12-week core treatment part



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.

12-week core treatment part, [redacted] for the pcJIA study

- A first sequential, ascending dose-cohort, 12-week, 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) [redacted]
- A second portion where approximately [redacted]
- A third portion (pcJIA only) where approximately [redacted]

Dose-finding portion: After a screening phase of up to 4 weeks (+ 3 days), patients will be included [via centralized Interactive Voice/Web Response System (IVRS/IWRS)] in one of 3 possible dose groups, in an ascending fashion, within a weight group, and treated for 12 weeks. [redacted]

The second portion: After sufficient 12 weeks data on PK, PD, efficacy and safety having been observed from the dose-finding portion, a dose will be selected for each weight group for more detailed investigation. [redacted]

The third portion[redacted] Approximately [redacted] 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.

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).

- [redacted]
- [redacted]

Extension part

Following the 12-week core treatment period, for the dose-finding and second portions, patients who have achieved a JIA ACR30 response [redacted] will continue in a 144-week extension phase; for the third portion in the pcJIA study, patients will continue in an 84 week extension phase. For patients enrolled prior to the dose selection (ie, dose-finding portion), they will continue on the same dose regimen of sarilumab they were assigned to receive in the 12-week part of the study until the dose regimen is selected. Once the dose regimen is selected, patients who were not already on this dose regimen will have their doses adjusted. The dose (mg) to be administered to a patient will be calculated at baseline and will remain the same throughout the course of the 12-week core part of the study. During the extension phase, however, the patient's weight will be measured at each visit and the dose will be modified (increase only) accordingly. The dose will be capped at 150 mg for dose regimens 1 (q2w) and 3 (qw) and 200 mg (q2w) for dose regimen 2, respectively.

Patients who discontinue the study treatment prematurely will be assessed using the procedure planned for the End of Treatment (EOT) visit. These patients will be asked to return for the End of Study (EOS) assessment 6 weeks after the EOT visit. For EOT during the 12-week core part, there will be an additional PK assessment 2 weeks after the EOT visit for the dose-finding and second portions (not applicable for the third portion in pcJIA study).

The total maximum duration of participation for a patient in these studies will be 166 weeks for patients enrolled in dose-finding and second portions and up to 106 weeks for patients enrolled in the third portion (pcJIA only):

- Up to 4 weeks of screening (maximum 31 days),

- 12 weeks core treatment period,
- Up to 144 weeks extension phase for patients enrolled in dose-finding and second portions and up to 84 weeks extension phase for patients enrolled in the third portion (pcJIA only), and
- 6 weeks post-treatment follow-up.

Beside the ongoing DEC and DMC reviews of PK, PD, safety and efficacy data for futility and dose escalations, two formal interim analyses for the [redacted] study and three formal interim analyses for the pcJIA study will be performed. Details are provided in Section 3.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of these studies is to describe the PK profile of sarilumab in patients with pcJIA (DRI13925) or [redacted] in order to identify the dose and regimen for adequate treatment of these pediatric populations.

1.2.2 Secondary objectives

The secondary objectives of these studies are to describe the pharmacodynamic (PD) profile, the efficacy and the long-term safety of sarilumab in patients with pcJIA[redacted].

[redacted]

[redacted]

[redacted]

[redacted]

1.4 STUDY PLAN

A brief description of the study design is provided in Section 1.1. The planned study schedules can be found in Section 1.2 Study Flow Charts of the protocols[redacted]

[redacted]

[redacted]

[redacted]

2 STATISTICAL AND ANALYTICAL PROCEDURES

[redacted]

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value prior to the first dose of study medication unless otherwise specified.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.1.5).

The below variables will be summarized by dose regimen cohort, overall and within each weight group.

Demographic characteristics

The demographic variables are

- Gender: Male, Female
- Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Reported, Unknown
- Age in years: quantitative and qualitative variable: 1 or 2 to 11 (children), 12 to 17 (adolescents)
- Ethnicity: Hispanic, non-Hispanic
- Region
- Tanner Stage

Medical and surgical history

Medical and surgical history includes all the relevant findings within the life-time of the patient. These data will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) using the version of the Medical Dictionary for Regulatory Activities (MedDRA) in use at Sanofi at the time of database lock (DBL).

Disease characteristics at baseline

Disease characteristics at baseline include:

- Duration of pcJIA[redacted] (weeks / months / years)
- For pcJIA only: Rheumatoid factor (Positive: ≥15 IU/mL, negative: <15 IU/mL)
- Absolute Neutrophil Count
- The following American College of Rheumatology (ACR) classification criteria components:
  - Number of joints with active arthritis
  - Number of joints with limited range of motion
  - hs-CRP and ESR
- Patient's assessment of physical function based on the Childhood Health Assessment Questionnaire (CHAQ)
- [redacted]
- For pcJIA, type of juvenile idiopathic arthritis (JIA) subset and medical history of uveitis

Vital signs and body measurements

Vital signs and body measurements at baseline include:

- Weight in kilograms (quantitative and qualitative variable: <30 kg, ≥30 kg)
- Height (cm)
- Body mass index (BMI; quantitative and qualitative variable: <25, ≥25 to < 30, ≥30 kg/m^2)
- Blood pressure (mmHg)
- Heart rate (bpm)
- Body temperature (°C).

Any technical details related to computation, dates, and imputations for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

All medications taken within a certain period of time before inclusion and until the end of the study, including biologics and vaccines taken since birth, immunosuppressive agents taken since diagnosis of pcJIA[redacted] (especially methotrexate (MTX), sulfasalazine, leflunomide, hydroxychloroquine, and folic/folinic acid taken within 3 months before screening), and all other medications taken within 3 months before screening are to be reported in the CRF pages.

All medications will be coded using the version of the World Health Organization-Drug Dictionary (WHO-DD) in use at Sanofi at the time of DBL.

- Prior medications are those the patient used within the 4 months prior to first investigational medicinal product (IMP) intake. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- In general, concomitant medications are any treatments received by the patient concomitantly to the IMP, from first dose of IMP to the end of treatment + 60 days. However, for non-steroidal anti-inflammatory drugs (NSAIDs), steroids, and disease-modifying antirheumatic drugs (DMARDs) given as treatment for JIA, any medication recorded at the baseline visit will be considered concomitant. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-study period (as defined in the observation period in Section 2.1.4).
- Post-study medications are those the patient took in the post-study period (as defined in the observation period in Section 2.1.4).

Any technical details related to computation, dates, and imputations for missing dates are described in Section 2.5.

2.1.3 Pharmacokinetic variables

The primary endpoint is sarilumab PK exposure (C_{max} and $AUC_{0-\tau}$), following first dose, and C_{trough} from baseline to week 12.

The PK blood samples will be collected before IMP injection at a given visit according to the schedules of sample collection and at or near the onset and completion of the occurrence of a serious adverse event (SAE). Details can be found in Section 1.2 Study Flow Charts of the protocols [redacted]

In the extension part, the main PK parameter will be serum sarilumab C_{trough}.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (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 part of the studies.

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 as below):

- The SCREENING epoch is defined as the time from the signed informed consent date up to the time prior to first dose of IMP.
- The CORE TREATMENT epoch is defined as the time from first dose of IMP to last dose in core phase +13 days for patients on bi-weekly dosing or +6 days for patients on weekly dosing, or first dose of IMP in the extension period for patients who enter the extension.
- 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 for patients on bi-weekly dosing or +6 days for patients on weekly dosing. Only patients who enter the extension have the EXTENSION TREATMENT epoch.
- The FOLLOW-UP epoch is defined as the time from the end of TREATMENT epoch (ie, the end of CORE TREATMENT epoch for patients not entering in the extension period; or the end of 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".

[redacted]

The entire treatment-emergent adverse event (TEAE) period includes the CORE TREATMENT, EXTENSION TREATMENT (only applicable for patients who enter the extension), and FOLLOW-UP epochs. The TEAE period for the core part includes CORE TREATMENT epoch for patients who enter the extension, and includes CORE TREATMENT and FOLLOW-UP epochs for patients not entering the extension.

2.1.4.1 Adverse events variables

Adverse event observation period

- Pretreatment AEs are AEs that developed or worsened or became serious during the screening epoch.
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened or became serious during the treatment and/or follow-up treatment epochs, as applicable.
- Post-study AEs are AEs that developed or worsened or became serious during the post-study epoch.

All AEs (including SAEs and AESIs) will be coded to a lower-level term (LLT), PT, high-level term (HLT), high-level group term (HLGT), and associated primary SOC using the version of MedDRA in effect at Sanofi at the time of DBL.

The occurrence of all AEs (including SAEs and AESIs) will be recorded from the time of signed informed consent until the end of the study.

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

Adverse events of special interest:

Two sets of summaries on adverse events of special interest (AESIs) will be generated:

1. One refers to AESIs for the pediatric program, as defined in the protocols. The AESIs and its search criteria are listed in Table 4.
2. To further ensure that all potential risks are fully evaluated, the AESIs defined in sarilumab adult RA program with search criteria broader than the AESI specified in the protocols will also be summarized. The AESIs and its search criteria are listed in Table 5.

Adverse events of special interest will be flagged in the database using search criteria. All AEs captured on the general AE form and any specific AE forms will be searched.

Table 4 – Protocol defined AESIs and search criteria

AESI flag	Search criteria
Clinically significant infections including: • Opportunistic infections • Tuberculosis	Reported by the investigators on the AE CRF page with AESI box ticked.
Anaphylaxis	
GI diverticulitis and perforation	
Lab abnormalities including: • ALT 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	
[redacted]	
[redacted]	
[redacted]	
[redacted]	
Pregnancy[a]	CRF checkbox: Pregnancy
Overdose[a]	CRF checkbox: Symptomatic overdose

a Standard AESI applies to all Sanofi studies

Table 5 - AESI and search criteria

AESI flag	Search[a] criteria
Leukopenia	SMQ: Haematopoietic leukopenia
Thrombocytopenia	SMQ: Haematopoietic thrombocytopenia
Infections (Opportunistic infections, Tuberculosis)	Primary SOC: Infections and infestations (CRF checkbox: Opportunistic infections; HLT Tuberculosis infections)
Hepatic disorders	SMQ : Drug-related hepatic disorders – comprehensive search
Diverticulitis/potential GI perforations[b]	SMQ: Gastrointestinal perforation and HLT: Diverticulum inflammations
GI ulcerations	SMQ: Gastrointestinal ulceration
Elevation in lipids	SMQ: Dyslipidemias
Anaphylaxis	SMQ: Anaphylactic reaction
Hypersensitivity	SMQ: Hypersensitivity
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Malignancy	SMQ: Malignant or unspecified tumours
Pregnancy[c]	CRF checkbox: Pregnancy
Overdose[c]	CRF checkbox: Symptomatic overdose

a All SMQs are narrow search
b These events will be further reviewed to identify cases of GI perforations
c Standard AESI applies to all Sanofi studies

2.1.4.2 Deaths

The death observation periods are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period
  - Death on-treatment: deaths occurring during the treatment epoch (ie, both Core and Extension treatment epoch if applicable)
  - Death during follow-up: deaths occurring during the follow-up epoch
- Death post-study: deaths occurring after the end of the study

2.1.4.3 Acceptability assessments (local tolerability)

The patient acceptability and local tolerability (HLT of injection site reactions) will be evaluated by the following parameters:

- Presence or absence of bruising, erythema, swelling, warmth, burning, stinging, itching, hive formation, pain, indurations, mass, discoloration, inflammation and other
    - Mild: Was able to perform normal activities, but was uncomfortable
    - Moderate: Was unable to perform some/many/most activities up to normal standards
    - Severe: Was completely unable to perform some/many/most activities

2.1.4.4 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology and clinical chemistry, and urinalysis. Clinical laboratory values will be converted to standard international units; international units will be used in all listings and tables. In addition, the lipid parameters will also be summarized in US units.

Schedule of blood samples for clinical laboratories can be found in Section 1.2 Study Flow Charts of the protocols [redacted]

The laboratory parameters will be classified as follows:

- Hematology
    - **Red blood cells and platelets**: hemoglobin, hematocrit, red blood cell (RBC) count and morphology (if RBC count is abnormal), platelet count
    - **White blood cells:** white blood cell (WBC) count, differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), absolute neutrophil count (ANC)
- Clinical chemistry
    - **Metabolism:** total protein, albumin
    - **Fasting lipids:** triglycerides (TG), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol
    - **Electrolytes**: sodium, potassium, chloride, bicarbonate, calcium, phosphate
    - **Renal function**: blood urea nitrogen (BUN), creatinine, creatinine clearance (using the equation of Schwartz for patients ≤ 18 years old and the equation of MDRD when patients grow to >18 years old)
    - **Liver function**: alanine aminotransferase (ALT) (SGPT), aspartate aminotransferase (AST) (SGOT), alkaline phosphatase (ALP), total, conjugated, and unconjugated bilirubin, [redacted]

[redacted]

Note: Whole chemistry at baseline and week 12 (or EOT) only. At all other visits: albumin, [redacted] ALT, AST, ALP, and total, conjugated, and unconjugated bilirubin only.

- **Glycosylated Hemoglobin HbA1C** (screening only): levels will be measured based on the patient's medical history and investigator's judgment
- **hs-CRP and ESR**
- **Pregnancy test**: for females who have commenced menstruating, a serum test is mandatory at screening and urine tests prior to IMP exposure at other indicated visits and EOT
- **Optional: Epstein Barr Virus (EBV)**, **Hepatitis screen, HIV** (screening only): EBV titer including IgG and IgM, hepatitis B surface antigen (HBs-Ag), hepatitis B surface antibody (HBs-Ab), hepatitis B core antibody (HBc-Ab), and hepatitis C antibody (HCV-Ab)
- **Rheumatoid Factor** (baseline only for pcJIA)

Urine samples for urinalysis will be collected at screening only:

- **Urinalysis (dipstick)**: pH, specific gravity, proteins, glucose, blood, nitrates, leukocyte esterase, bilirubin

  Note: If any parameter on the dipstick is abnormal, a urine sample will be sent to the central laboratory for testing. If positive for proteins, microscopic analysis will be performed by the central laboratory.

Technical formulas are described in Section 2.5.1.

2.1.4.5 Vital signs variables

Vital signs include heart rate, systolic and diastolic blood pressure (SBP and DBP), temperature, height, and weight. At each visit where blood pressure is scheduled, two assessments, at least 1 minute apart, will be performed and recorded according to procedures described in the protocol.

The schedule of vital sign assessments can be found in can be found in Section 1.2 Study Flow Charts of the protocols [redacted]

2.1.4.6 Anti-body/Serology variables

Antinuclear antibodies/anti-ds DNA will be measured at baseline and weeks 12, 24 and then every 24 weeks up to the EOT visit.

2.1.5 Efficacy endpoints

The primary endpoint for these studies is PK exposure, and efficacy endpoints are secondary. Efficacy assessment will be performed as described below.

The evaluation schedule for efficacy variables can be found in Section 1.2 Study Flow Charts of the protocols [redacted]

Note that all efficacy evaluations up to the closeout measurement will be included for analysis unless otherwise specified. Baseline for efficacy variables is defined as the last non-missing value on or before the date of inclusion (assigned treatment). For patients who have no value on or before the inclusion date, the last non-missing value on or before the date of first IMP intake will be used as baseline.

2.1.5.1 JIA ACR30 response

The definition for JIA ACR30 response[redacted] is ≥3 out of the 6 JIA core set variables with ≥30% improvement from baseline with no more than 1 of the remaining variables worsened by ≥30%. The core set variables include:

- **Physician global assessment of disease activity**: assessed on an anchored 100 mm horizontal visual analogue scale (VAS) where 0 is considered the best disease activity (no disease activity) and 100 the worst (most disease activity)
- **Parent or patient assessment of overall well-being**: rated on an anchored 100 mm horizontal VAS where 0 is considered the best disease activity (no disease activity) and 100 the worst (most disease activity)
- **Number of joints with active arthritis**
- **Number of joints with limited range of motion**
- **Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI)**: The CHAQ is a generic measure of health status in children ages 1 to 19 years of age which can be interviewer or self-administered for children ≥ 8 and parent/proxy-administered for children younger than 8 years of age. The questionnaire, with the past week as the time frame, is used to assess functional ability of patients with JIA in 8 domains: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Each item is scored on a four point scale ranging from 0 to 3: 0 (without any difficulty), 1 (with some difficulty), 2 (with much difficult), and 3 (unable to do). An additional response of "not applicable" is available to indicate activities the patient is unable to perform because he/she is too young. The mean score of the eight domains makes up the disability index and ranges from 0 (no disability) to 3 (disabled). A CHAQ-DI score cannot be calculated validly when there are scores from less than 6 of the 8 categories. Note that items marked as not applicable are not considered in the score calculation. The disability index is supplemented with two VAS scores. The CHAQ – discomfort index rates the severity of

pain in the past week and the CHAQ health status score measures the parent or proxy's global assessment of health status, both using a 0-100 VAS scale.

- **Index of inflammation**: hs-CRP

[redacted]

2.1.5.2 Other secondary efficacy endpoint(s)

In addition to the assessment of responders as per the definition stated above, the other secondary efficacy endpoints for the 12-week core part are the change from baseline at week 12 in the 6 individual JIA ACR components, and JIA ACR30 response at week 12 using ESR instead of hs-CRP. Additional efficacy endpoints are listed as follows.

12-week core part:

- JIA ACR 50/70/90/100 proportion responders at week 12: ≥3 out of the 6 JIA core set variables with ≥50/70/90/100% improvement from baseline with no more than 1 of the remaining variables worsened by ≥30%; [redacted]
- Juvenile Arthritis Disease Activity Score-27 (JADAS-27) change from baseline at Week 12

Extension part:

- JIA ACR 30/50/70/90/100 proportion responders at weeks 24, 48, and every 24 weeks up to the end of the study
- JADAS-27 change from baseline at weeks 24, 48, and every 24 weeks up to the end of the study
- [redacted]

The JADAS includes 4 measures:

- Physician global assessment of disease activity (as previously defined)
- Parent or patient assessment of overall well-being (as previously defined)

- Count of joints (27) with active disease
- Index of inflammation: hs-CRP or ESR level
  - ESR normalized to a 0-10 scale according to the following formula: (ESR[mm/hour]-20)/10 where before making the calculation, ESR value <20 mm/hour converted to 0 and ESR value >120 mm/hour converted to 120.
  - Or hs-CRP normalized to a 0-10 scale according to the following formula: (CRP [mg/L] – 10)/10 where before calculation, CRP values <10 mg/L were converted to 0 and CRP values >110 mg/L were converted to 110.

The JADAS-27 will be calculated as the simple linear sum of the scores of its 4 components.

[redacted]

[redacted]

2.1.7 Immunogenicity endpoints

The ADA blood samples will be collected before injection during the same visit according to the schedules of sample collection and at or near the onset and completion of the occurrence of an SAE. Details can be found in Section 1.2 Study Flow Charts of the protocols [redacted]

At each sample time point, the result of an analyzed sample in the antidrug antibody (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.

A treatment-emergent positive response is further classified as persistent or transient.

- Persistent ADA Response: treatment-emergent ADA detected at 2 or more consecutive post-treatment sampling time points, where the first and last ADA positive samples are separated by a period of at least 16 weeks. Also persistent in the case where the last sample analyzed is positive, regardless of any other time points.
- Transient Response: A treatment-emergent response that is not considered persistent.

2.1.8 Pharmacodynamic/Pharmacogenomic endpoints

The PD endpoints include changes from baseline at week 12 (or EOT) in IL-6 associated biomarkers (eg, serum levels of hs-CRP, IL-6, sIL-6R).

Genomic analysis will be performed in a subset of patients (separate informed consent) using a saliva sample collected at baseline (and potentially other study visits). The description of endpoints and analyses will be included in a separate document.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

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 informed consent form 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 clinical study report 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 part
- Patients completing the study treatment per protocol
- Patients not completing the study treatment period as per protocol
- Patients discontinuing study treatment by main reason for permanent treatment discontinuation
- Patients entering the extension part
- Status at last study contact

For each study [redacted] disposition will be summarized by dose regimen cohort, overall and within each weight group. For all categories of patients (except for the screened), percentages will be calculated using the number of included patients as the denominator. Reasons for treatment discontinuation will also be provided by dose regimen cohort within center and/or region. At the final analysis, patient disposition in the extension part will be included.

A patient is considered lost to follow-up at the end of the study if he/she is not assessed at the last protocol planned visit and if the time from the last successful contact to the last protocol planned visit is greater than 3 days.

All critical or major deviations and inclusion and drug-dispensing irregularities will be summarized in tables giving numbers and percentages of deviations for each dose regimen cohort, overall and within each weight group.

Additionally, the analysis populations for safety, efficacy, PK, and PD will be summarized in a table by number of included patients.

- Efficacy population
- Safety population
- PK/PD/Immunogenicity population.

2.2.1 Randomization and drug dispensing irregularities

Inclusion is used here in place of randomization given these are open label, ascending dose studies. Inclusion and drug-dispensing irregularities occur whenever:

1. An inclusion is not in accordance with the protocol-defined inclusion method, such as a) an ineligible patient is included, or b) a patient is included twice.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined method, such as a) a patient at any time in the study is dispensed a different treatment kit than as assigned (which may or may not contain the correct-as-included IMP), or b) a non-included patient is treated with IMP reserved for included patients.

Inclusion and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All inclusion and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among included patients (number and percentages).

Inclusion and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Table 6 - Inclusion and drug allocation irregularities

Kit dispensation without IVRS/IWRS transaction
Erroneous kit dispensation
Kit not available
Inclusion by error
Patient included twice
Patient switched to another site

2.3 ANALYSIS POPULATIONS

The all treated population comprises any patient with a signed informed consent and received at least one dose of the IMP.

2.3.1 Pharmacokinetic, pharmacodynamics and immunogenicity population

The PK population will consist of all patients in the safety population with at least one post-dose, non-missing 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.

In all cases, patients will be analyzed according to the treatment actually received.

2.3.2 Safety population

The safety population will consist of all patients who 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 IMP will be included in the safety population according to the assigned treatment
- In case a patient receives 1 or more incorrect dose of sarilumab other than the one assigned, the dose regimen cohort allocation for as-treated analysis will be the dose regimen cohort in which he/she was treated for the longest duration.

2.3.3 Efficacy populations

The efficacy population will consist of all patients who received 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.

2.4 STATISTICAL METHODS

In general, summaries will be by study [redacted] except for the modeling of the PK data.

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum. For blood pressure, the average of the two SBP and the two DBP readings for a patient will be used for analysis. Categorical and ordinal data will be summarized using the number and percentage of patients.

Parameters described in Section 2.1.1 will be summarized for the all treated population by dose regimen cohort, overall and within each weight group.

Medical and surgical history will be summarized by dose regimen cohort, overall and within each weight group, according to primary SOC and PT, sorted by internationally agreed order of SOC and decreasing frequency of PT within SOC (based on the overall cohort in each study).

P-values for demographic and baseline characteristic data will not be calculated.

No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the all treated population as

- Prior medications discontinued before the first dose of IMP
- Prior medications that continued at the time of the first dose of IMP
- Concomitant medications.

Medications will be summarized by dose regimen cohort, overall and within each weight group, according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the generic names. Sorting will be by decreasing frequency of anatomic category followed by all other generic names based on the overall incidence in the total cohort, for each study separately. In case of equal frequency regarding anatomic categories

(respectively generic names), alphabetical order will be used. All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic) linked to the medication. Therefore patients may be counted several times for the same medication.

The following summaries will also be provided:

- Vaccines (prior and concomitant, separately)
- Concomitant non-biological DMARDs (MTX, sulfasalazine [SSZ], leflunomide [LEF], hydroxychloroquine [HCQ]), folic acid, NSAIDs, and corticosteroids
- Prior DMARDs (biological and non-biological) taken since diagnosis of JIA and discontinued before the first dose of IMP

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual IMP dose regimen cohort, overall and within each weight group, using the safety population (Section 2.3.2).

2.4.3.1 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 (+ 7 days for dose regimen 3 cohort). These calculations are regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum) and categorically by numbers and percentages of patients within each of the following categories and cumulatively according to these categories:

- 12-week core part
  - ≤6 weeks
  - >6 and ≤12 weeks
  - >12 weeks
- Final study data, including extension
  - ≤12 weeks (3 months)
  - >12 and ≤24 weeks
  - >24 and ≤ 36 weeks
  - >36 and ≤ 48 weeks

- >48 and ≤ 72 weeks
- >72 and ≤ 96 weeks
- >96 and ≤ 120 weeks
- >120 and ≤ 144 weeks
- >144 and ≤ 156 weeks
- >156 weeks

Additionally, the cumulative duration of treatment exposure, defined as the sum of patients' duration of treatment exposure expressed in patient years, will be provided.

The time between doses will be summarized.

2.4.3.2 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 defined in Section 2.1.4.

Treatment compliance 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 at least twice the assigned dose during an interval of less than 11 days for q2w dosing and less than 6 days for qw dosing. Symptomatic overdose will be reported as an AESI. More generally, dosing irregularities will be as listed in Section 2.2.1.

2.4.4 Analyses of pharmacokinetic variables

Serum trough concentrations of functional sarilumab will be summarized using descriptive statistics (including number, arithmetic and geometric means, SD, standard error of the mean (SEM), CV (%), minimum, median, and maximum) by dose regimen cohort, 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 every other week regimens; <5 days or >9 days before the sampling time for every week 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 the descriptive statistics mentioned above by immunogenicity status for each dose regimen cohort at each visit.

Listings of serum concentration will be provided for each individual patient including subject identification (ID), gender, age, first dose date, visit number, categorized time point (0 for trough level and 1 for pre-dose), date/time of previous dose, PK sampling date/time, duration since first dose (days), duration since previous dose (dd:hh), and serum concentration (mg/L).

All PK analyses will be performed using the PK population.

[redacted]

2.4.5 Analyses of safety data

Safety data will be summarized descriptively for each study [redacted] separately. The summary of safety results will be presented by dose regimen cohort. Further subdivision by weight group will be performed only for selected parameters given the small sample size.

Safety summaries during the entire TEAE period will be provided. In addition, summaries on the important safety events will also be provided by time periods including 0-12 weeks, 0-24 weeks, and 0-52 weeks; details are provided in Section 2.4.5.6. For the analyses on 0-52 weeks and entire TEAE period, summaries on the non-selected doses will only include the data collected prior to the first dose adjustment to the selected dose; a combined 'any dose' group will be added to summarize all the safety data for all treated patients. In addition, data after the dose adjustment will be summarized separately (Section 2.4.11).

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, 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 (Appendix A).

- 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 cohort on the safety population.
- For quantitative safety parameters based on laboratory measurements, descriptive statistics will be used to summarize result and change from baseline values by visit and dose regimen cohort. 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 IMP. 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.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of AE reporting will be on TEAEs. Pretreatment and post-study AEs will be described separately.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pretreatment, treatment-emergent, or post-study. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment emergent unless there is definitive information to determine it is pretreatment or post-study. Details on classification of AEs with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present the number (n) and percentage (%) of patients in each dose regimen cohort experiencing an AE by primary SOC (sorted by internationally agreed SOC order), HLGT, HLT, and 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 cohort. In addition, the incidence and the number of events per 100 patient-years (number of events adjusted for the total duration of exposure) will be provided for AE summaries during the entire TEAE period.

Sorting within tables ensures the same presentation for the set of all AEs within the observation period (pretreatment, treatment-emergent, and post-study). For that purpose, the table of all TEAEs presented by primary SOC and PT sorted by the internationally agreed SOC order and

decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the selected dose regimen cohort.

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE
  - Treatment-emergent SAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least one TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All TEAEs by primary SOC and PT, showing the number (%) of patients with at least one TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified.
- All TEAEs regardless of relationship and related by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least one TEAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All TEAEs by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least one TEAE by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above.

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent SAEs by primary SOC, HLGT, HLT, and PT, and also by primary SOC and PT, showing the number (%) of patients with at least one treatment-emergent SAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order for the 4-level summary.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All TEAEs leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, and also by primary SOC and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order for the 4-level summary.

Analysis of AESIs

Summaries of AESIs (Section 2.1.4.1) include:

- All treatment emergent AESIs, by AESI category and PT, showing number (%) of patients, sorted by decreasing incidence of PT within each AESI category.
- Within each treatment emergent AESI category, at a minimum, the data display will include:
  - Overview summary
  - Treatment duration summary
  - Incidence by patient and by event
  - Treatment emergent SAEs
  - TEAEs leading to treatment discontinuation
  - TEAEs leading to death
  - Possibly related TEAEs

2.4.5.2 Deaths

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.

Listings will be provided for all deaths with flags indicating on-treatment, during follow-up or post-study status.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, SD, 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 cohort. This section will be organized by biological function as specified in Section 2.1.4.4.

In addition, for all laboratory parameters, the mean value and mean change from baseline at each scheduled visit will be plotted by dose regimen cohort.

The incidence of PCSAs (Appendix A) at any time during the TEAE period will be summarized by biological function and dose regimen cohort whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria.

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

The incidence of PCSAs at any time during the post-study period will be summarized by the actual dose regimen cohort received in the 12-week core treatment period.

The incidence of abnormal laboratory values at any time during the TEAE period will be summarized in shift tables by biological function and dose regimen cohort whatever the baseline level and/or according to the following baseline status categories:

- Normal/Missing
- Abnormal high according to the normal range
- Abnormal low according to the normal range

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

Neutrophils

The incidence of neutropenia will be summarized by maximal grade (lowest absolute neutrophil count reported during the TEAE period):

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

For patients with Grade 3 or 4 neutropenia, a listing with the individual neutrophil counts, WBC counts, platelet counts, lymphocytes, and hemoglobin at each visit (including re-tests taken at either central or local labs) will be provided.

The neutrophil counts at each scheduled visit during the study will be plotted by dose regimen cohort. In addition, summaries will include the following data: discontinuation, restart dosing, dosing delay, number of episodes, and normalization (to >1 x LLN or return to baseline if baseline <LLN). Laboratory measurements during the post-study period will be considered in the analysis of normalization.

Thrombocytopenia

The incidence of thrombocytopenia will be summarized by maximal grade (lowest platelet count reported during the TEAE period):

- Grade 1: ≥75 Giga/L-100 Giga/L
- Grade 2: ≥50 Giga/L-75 Giga/L
- Grade 3: ≥25 Giga/L-50 Giga/L
- Grade 4: <25 Giga/L

Lymphopenia

The incidence of lymphopenia will be summarized by maximal grade (lowest lymphocyte count reported during the TEAE period):

- Grade 1: ≥0.8 Giga/L-LLN
- Grade 2: ≥0.5 Giga/L-0.8 Giga/L
- Grade 3: ≥0.2 Giga/L-0.5 Giga/L
- Grade 4: <0.2 Giga/L

Hepatic disorders

The liver function tests (LFTs), namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by dose regimen cohort 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 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

The normalization (to <1 x ULN) or return to baseline (in case of baseline >ULN) of elevated LFTs will be summarized by categories of elevation (>3 x ULN, >5 x ULN, >10 x ULN, >20 x ULN for ALT and AST; >1.5 x ULN for ALP; and >1.5 x ULN and >2 x 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 part); 3) normalized after last dose; 4) last value not normal. Laboratory measurements 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.

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, SD, 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 cohort. The average of the two SBP and the two 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 cohort whatever the baseline level and/or according to the following baseline status categories:

- Normal/Missing
- Abnormal according to PCSA criterion or criteria

Listings will be provided with flags indicating the PCSA values.

2.4.5.5 Analysis of anti-body/serology endpoints

Assessment of ANA/anti-ds DNA will be summarized by visit for each dose regimen cohort, overall and by weight group.

[redacted]

[redacted]

[redacted]

2.4.6 Analyses of efficacy endpoints

Efficacy is considered as secondary in these studies, and will be summarized descriptively for each study (ie, disease type) separately.

Efficacy analyses will be done by dose regimen cohort and by weight group. Summaries on the non-selected doses will only include the data collected prior to the first dose adjustment to the selected dose. Data after the dose adjustment will be summarized separately (Section 2.4.11).

2.4.6.1 Analysis of JIA ACR30 response

Patients achieving JIA ACR30[redacted] response for each dose regimen cohort, overall and by weight group, will be summarized by visit using counts, proportions and 95% CIs. The primary approach will be based on all observed data while the patient remains on treatment. No missing data will be imputed.

Additionally, for the summaries on the JIA ACR30 responses during the 12-week core treatment part, several different approaches will be used for the handling of treatment discontinuations and missing data.

Non-responder imputation approach:

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 (sensitivity analysis), the missing data will be imputed using the last observation carried forward (LOCF) procedure from the point of treatment discontinuation for all 6 ACR components [redacted] 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 the analysis. No missing data will be imputed.

Subgroup analyses:

No additional subgroup summaries are planned for efficacy.

2.4.6.2 Analyses of other efficacy endpoints

JIA 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. JIA ACR30 response using ESR instead of hs-CRP will be summarized using the same methods as described in the previous section.

JIA ACR50/70/90/100 [redacted] responses will be summarized using the same methods as described above for JIA-ACR30.

Overall score and change from baseline in JADAS-27 will be summarized by visit (including number, mean, standard error, SD, median, minimum, and maximum) for each dose regimen cohort and weight group (if possible).

Proportions of patients with the low disease activity (JADAS-27≤3.8) and inactive disease activity (JADAS-27≤1.0) as defined based on JADAS-27 will be explored and summarized. The Kaplan-Meier plot for time to first onset of achieving low disease activity or achieving inactive disease will also be provided.

For the analyses of continuous endpoints including JIA ACR core set variables and JADAS-27, no data will be imputed and the analyses will be done based on data as observed while the patient remains on treatment.

[redacted]

2.4.6.3 Multiplicity issues

No formal hypothesis testing will be performed.

[redacted]

[redacted]

2.4.8 Analysis of immunogenicity variables

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 transient treatment-emergent ADA positive patients
  - Number (%) of neutralizing antibody
  - Number (%) of non-neutralizing antibody
- Number (%) of persistent treatment-emergent ADA positive patients
  - Number (%) of neutralizing antibody
  - Number (%) of neutralizing antibody
- 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 regimen cohort. Persistent and transient ADA responses may be investigated during the extension phase of the trial where multiple ADA assessments are available.

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 cohort.

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

In addition to the summaries and plots described above, individual, spaghetti, and/or other plots of relevant PK, ADA, and efficacy data may be produced to aid in the visualization/interpretation of the data.

2.4.9 Analyses of pharmacodynamic variables

Serum concentrations of IL-6, sIL-6Rα and hs-CRP will be summarized using descriptive statistics (including number, arithmetic and geometric means, SD, SEM, CV (%), minimum, median and maximum) by dose regimen cohort and weight group for each visit.

[redacted]

Appendix C provides mock-up tables to illustrate how the safety events and efficacy endpoints will be summarized before and after dose adjustment in the clinical study reports.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas:

Age at baseline is calculated as follows:

Age = (informed consent date – birth date)/365.25

BMI is calculated as follows:

BMI = Weight in kg/(height^2 in meters).

Renal function formulas:

Creatinine clearance (CLcr) values will be derived using the equation of Schwartz

- female patients 1-18 years of age and male patients < 13 years of age

  CLcr (mL/min/1.73m^2) = (height (cm) * 0.55)/creatinine (mg/dL)

- male patients ≥ 13 years of age

  CLcr (mL/min/1.73m^2) = (height (cm) * 0.7)/creatinine (mg/dL)

For patients grow to >18 years old, the equation of Modification of Diet in Renal Disease (MDRD) will be used (non-Black will be assumed if Race is missing):

- CLcr (mL/min/1.73m^2) = 175 * creatinine (mg/dL)$^{-1.154}$ * Age$^{-0.203}$ * 1.212 (if Black) * 0.742 (if Female)

2.5.2 Data handling conventions for secondary efficacy variables

JIA-ACR component – joint counts with active arthritis/limited range of motion (AJC/LJC)

When calculating the AJC and LJC, the joints with missing assessment will be imputed as the mean of the joints with assessment, ie, the AJC/LJC after imputation are as follows:

AJC = sum (joints with active arthritis='Y')*(71/number of joints with assessment)

LJC = sum (joints with limited motion='Y')*(67/number of joints with assessment)

Please note: the imputation will only be performed if the number of joints with missing assessment is ≤7 for each active arthritis or limited motion joints. If the number of joints with missing assessment is >7, then the corresponding joint counts will be set to missing.

JADAS-27 component – joint counts (27) with active arthritis (AJC27)

When calculating the AJC27, the joints with missing assessment will be imputed as the mean of the joints with assessment, ie, the AJC27 after imputation is as follows:

AJC27 = sum (joints with active arthritis='Y')*(27/number of joints with assessment)

Please note: the imputation will only be performed if the number of joints with missing assessment is ≤3 for 27 joints. If the number of joints with missing assessment is >3, then AJC27 will be set to missing.

JIA-ACR component - CHAQ-DI

The CHAQ questionnaire consists of 30 questions referring to eight domains; dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities. Each domain has at least two component questions and there are five possible responses (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, 3 = unable to do, and "not applicable"). If any of the questions contain multiple responses, the worst case in terms of a patient's health status will be assumed, this being the most conservative approach. A domain score is determined from the highest score (ie, worst response) of the questions in that domain. However, if specific aids and devices are used or assistance from another person is required in performing functional tasks, then the score of the respective domain is adjusted. If the domain score is 0 or 1, then the domain score is increased to 2, and if the domain score is 2 or 3, then the domain score is not adjusted. To calculate the overall CHAQ-DI score the patient must have a domain score for at least six of the eight domains. The CHAQ-DI score is the sum of the domain scores divided by the number of domains that have a non-missing score. This overall score ranges from 0 (best) to 3 (worst). Note that items marked as not applicable are not considered in the score calculation.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of computation of treatment duration if investigational drug end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the dosing CRF page. If this date is missing, the exposure duration will be kept as missing.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing such that it cannot be determined whether it was taken prior or concomitantly, it will be considered as a prior and concomitant medication.

Handling of AEs with missing or partial date/time of onset

Missing or partial AE onset dates and times will be imputed so that if the partial AE onset date/time information does not indicate that the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment-emergent. No imputation of AE end dates/times will be performed. These data imputations are for categorization purposes of treatment emergence only and will not be used in listings. No imputation is planned for date/time of AE resolution.

Handling of AE when date and time of first IMP date is missing

When the date and time of the first IMP is missing, all AEs that occurred after or on the day of inclusion will be considered as TEAEs. The exposure duration will be kept as missing.

Handling of missing relationship to IMP of AEs

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the AE considered as such in the frequency tables of possibly related AEs, but no imputation will be done at the data level.

Handling of missing severity of AEs

If the severity is missing for one of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

Handling of PCSA

If a subject has a missing baseline, he/she will be grouped in the category “normal/missing at baseline”.

For PCSA with two conditions, one based on a change from baseline value or a normal range and the other one on a threshold value, the first condition being missing, the PCSA will be based only on the second condition.

For PCSA defined on a threshold and/or a normal range, the PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is >0.5 Giga/L or >ULN if ULN ≥0.5 Giga/L. When ULN is missing, the value 0.5 Giga/L will be used.

Measurements flagged as invalid by the laboratory will not be summarized nor be taken into account in the computation of PCSA values.

2.5.4 Windows for time points

For efficacy parameters, discontinuation visit will be mapped to the scheduled visit for the analyses. If a discontinuation visit happens at a regular visit, then the visit number will be reassigned as the regular visit number where an assessment is planned. If a discontinuation visit happens between 2 regular visits, then the visit number will be reassigned to the next visit number where an assessment is planned. For example, if a discontinuation visit happens between Visits 5 and 6, then the visit number will be reassigned as 6.

Visit windows based on days relative to the first IMP dose will be used to map the laboratory values, vital signs, ADA, and PK measurements to each scheduled visit (see Appendix B for details). The following rule will be applied when mapping the measurements to the visit:

1. When a patient has more than one measurement on the same lab parameter (or vital sign) on the same date, then the one with the later/largest sample ID will be used.
2. For the same laboratory parameter (vital sign), if a patient has more than one measurement at different dates within the same visit window, the scheduled measurement that is closest to the target date will be used. If there is no scheduled measurement within the visit window, the unscheduled measurement that is closest to the target date will be used.
3. When a patient has more than one measurement on the same lab parameter with the same distance from the target date, the one with the latest date will be used.

2.5.5 Unscheduled visits and local laboratory measurements

For the by-visit laboratory parameters summary and the PCSA analysis, laboratory measurements performed at both central and local labs will be used.

Unscheduled visit measurements of vital signs and laboratory parameters will be included in the by-visit summaries using specified visit windows.

2.5.6 Pooling of centers for statistical analyses

Pooling by region may be performed, but to be determined.

2.5.7 Statistical technical issues

None.

3 INTERIM ANALYSIS

A DMC, composed of independent pediatric rheumatologists who are not participants in the sarilumab pediatric clinical studies, are not sponsor representatives, and do not have any conflict of interest with regard to study outcomes, will monitor patient safety by conducting formal reviews of accumulated safety data and will recommend the appropriate course of action for the study to a DEC, composed of sponsor representatives. The DMC members' responsibilities and the process for data review are described in the DMC Charter.

The DEC 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, subject to the DMC recommendations regarding safety. The DEC members' responsibilities and the process for data review are described in the DEC Charter.

[redacted]

In addition to this ongoing review of data for dose escalation and futility, [redacted] three formal interim analyses for pcJIA will be performed prior to the conclusion of the extension part for all patients:

- The first formal interim analysis will be performed once sufficient Week 12 data have been observed from the dose-finding portion to allow a selection of a dose regimen for more detailed investigation.
- Second interim analysis will be performed approximately one year from the time every patient enrolled in the dose-finding and second portions has started receiving 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.
- Third interim analysis (pcJIA only) will be performed approximately 1 year from the time the last patient enrolled in the third portion.

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.

4 DATABASE LOCK

The first database lock will occur approximately 4 weeks after sufficient Week 12 data have been observed from the dose-finding portion.

The second database lock will occur approximately 4 weeks after one year from the time every patient enrolled in the first and second portions has received the selected dose regimen (either new enrolled patients or patients already in the extension phase).

The third database lock (pcJIA only) will occur approximately 4 weeks after one year from the time the last patient enrolled in the third portion.

The final database lock, including the extension, will occur approximately 4 weeks after the last patient has completed the end of study visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.0 or higher.

6 REFERENCES

1. Wang Y, Jadhav PR, Lala M, Gobburu JV. Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. J Clin Pharmacol. 2012 Oct;52(10):1601-6.

2. Brunner HI, Ruperto N, Zuber Z, Keane C, Kenwright A, Lu P, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015 Jun;74(6):1110-7.

3. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012 Dec 20;367(25):2385-95.

4. World Health Organization [Internet]. Child growth standards: WHO Anthro (version 3.2.2, January 2011) and macros [cited 25 May 2017]. Available from: http://www.who.int/childgrowth/software/en/.

7 LIST OF APPENDICES

Appendix A: Criteria for potentially clinically significant abnormalities for studies in children

Appendix B: Visit windows based on day ranges for laboratory values, vital Signs, ADA, and PK measurements

Appendix C: Mock up tables for safety events and efficacy endpoints before and after dose adjustment

Appendix A Criteria for Potentially Clinically Significant Abnormalities for Studies in Children

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES For Studies in Children			
Parameter	**Age range**	**PCSA**	**Comments**
ECG parameters			Ref. : Rijnbeek P.R. et al., Eur Heart J 2001; Davignon A. et al., Ped Cardiol 1979/1980; Semizel E.et al., Cardiol Young 2008; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
HR	Birth/0 to 27 days old (Neonates)	≤90 bpm and decrease from baseline ≥20 bpm ≥190 bpm and increase from baseline ≥20 bpm	
	28 days/1 month to 23 months old (Infants)	≤80 bpm and decrease from baseline ≥20 bpm ≥175 bpm and increase from baseline ≥20 bpm	
	24 months/2 years to <6 years old (Children)	≤75 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm	
	6 to <12 years old (Children)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
	12 to 16/18 years old (Adolescents)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	Birth/0 to 27 days old (Neonates)	≥120 ms	
	28 days/1 month to 23 months old (Infants)	≥140 ms	
	24 months/2 years to <6 years old (Children)	≥160 ms	
	6 to <12 years old (Children)	≥170 ms	
	12 to 16/18 years old (Adolescents)	≥180 ms	
QRS	Birth/0 to 27 days old (Neonates)	≥85 ms	
	28 days/1 month to 23 months old (Infants)	≥85 ms	
	2 to <6 years old (Children)	≥95 ms	
	6 to <12 years old (Children)	≥100 ms	
	12 to 16/18 years old (Adolescents)	≥110 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
QTc	Birth/0 to <12 years old (Neonates, Infants, Children)	Absolute values (ms) Borderline: 431-450 ms Prolonged*: >450 ms Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	**To be applied to QTcF** *QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings.
	12 to 16/18 years old (Adolescents)	Borderline: 431-450 ms (Boys); 451-470 ms (Girls) Prolonged*: >450 ms (Boys); >470 ms (Girls) Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	
Vital Signs			Ref. : Kidney Disease Outcomes Quality Initiatives (KDOQI) Guideline 13; 1996; The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics 2004; Bowman E & Fraser S Neonatal Handbook 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Pediatric respiratory rates http://www.health.ny.gov/
SBP	Birth/0 to 27 days old (Neonates)	≤60 mmHg and decrease from baseline ≥20 mmHg ≥85mHg and increase from baseline ≥20 mmHg	Based on definition of Hypertension as average SBP or DBP ≥ 95th percentile for gender, age, and height on ≥ 3 occasions
	28 days/1 month to 23 months old (Infants)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥98 mmHg and increase from baseline ≥20 mmHg	
	24 months/2 years to <6	≤70 mmHg and decrease from baseline ≥20	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
	years old (Children)	mmHg ≥101mHg and increase from baseline ≥20 mmHg	
	6 to <12 years old (Children)	≤80 mmHg and decrease from baseline ≥20 mmHg ≥108 mmHg and increase from baseline ≥20 mmHg	
	12 to 16/18 years old (Adolescents)	≤90 mmHg and decrease from baseline ≥20 mmHg ≥119mmHg and increase from baseline ≥20 mmHg	
DBP	Birth/0 to 27 days old (Neonates)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥50mHg and increase from baseline ≥10 mmHg	
	28 days/1 month to 23 months old (Infants)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥54mHg and increase from baseline ≥10 mmHg	
	24 months/2 years to <6 years old (Children)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥59mHg and increase from baseline ≥10 mmHg	
	6 to <12 years old (Children)	≤48 mmHg and decrease from baseline ≥10 mmHg ≥72mHg and increase from baseline ≥10 mmHg	
	12 to 16/18 years old (Adolescents)	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78mHg and increase from baseline ≥10 mmHg	
Orthostatic hypotension	All age ranges	SBP : St — Su ≤ - 20 mmHg DBP : St — Su ≤ - 10 mmHg	
Temperature	All age ranges	Rectal, ear or temporal artery: ≥100.4 °F/38.0 °C Oral or pacifier: ≥99.5 °F/37.5 °C Axillary or skin infrared: ≥99 °F/37.2 °C	Ear temperature not accurate below 6 months of age
Respiratory rate	Birth/0 to 27 days old (Neonates)	< 30 per minutes > 60 per minutes	Based on normal range
	28 days/1 month to 23 months old (Infants)	< 24 per minutes > 40 per minutes	
	24 months/2 years to <6 years old (Children)	< 22 per minutes > 34 per minutes	
	6 to <12 years old (Children)	< 18 per minutes > 30 per minutes	
	12 to 16/18 years old (Adolescents)	< 12 per minutes > 20 per minutes	
Sa02	All age ranges	≤95 %	
Weight	All ranges	≥5 % weight loss from baseline	Based on identification of trends in the child's growth with a series of visits WHO Multicentre Reference

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
			Study Group, 2006; Center for Disease Control. Growth chart 2007
Clinical Chemistry			Ref Molleston JP et al. JPGN 2011; Moritz et al., Pediatrics 1999; Moritz et al., Pediatr Nephrol 2005 ; Sedlacek et al., Seminars in Dialysis 2006) Gong G et al. Clinical Biochemistry 2009; Masilamani et al. Arch Dis Children 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
ALT/SGPT	All age ranges	≥3 ULN By distribution analysis: ≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN	Based on normal ranges: 6 to 50 U/L (0-5 days), 5 to 45 U/L (1-19 years)
AST/SGOT	All age ranges	≥3 ULN By distribution analysis: ≥3 ULN ≥5 ULN ≥10 ULN ≥20 ULN	Based on normal ranges: 35 to 140 U/L (0-5 days), 15 to 55 U/L (1-9 years), 5 to 45 U/L (10-19 years)
Alkaline Phosphatase	All age ranges	≥1.5 ULN	Based on normal ranges: 145 to 420 U/L (1-9 years), 130 to 560 U/L (10-11 years), 200 to 495 U/L (Boys 12-13 years), 105 to 420 U/L (Girls 12-13 years), 130 to 525 U/L (Boys 14-15 years), 70 to 130 U/L (Girls 14-15 years), 65 to 260 U/L (Boys 16-19 years), 50 to 130 U/L (Girls 16-19 years)
Total Bilirubin	All age ranges	≥1.3 ULN	CF = mg x 1.7 = µmol Based on normal ranges: <6 mg/dL (Term 0-1 day), <8 mg/dL (Term 1-2 days), <12 mg/dL (Term 3-5 days), <1

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
			mg/dL (Term >5 days)
Conjugated Bilirubin	All age ranges	>35% Total Bilirubin and TBILI≥1.3 ULN	CF = mg x 1.7 = µmol Based on normal range: 0 to 0.4 mg/dL
ALT and Total Bilirubin	All age ranges	ALT ≥ 3 ULN and Total Bilirubin ≥ 2 ULN	
CPK	All age ranges	≥3 ULN	
Creatinine	Birth/0 to <6 years old (Neonates, Infants, Children)	>53 µmol/L or 0.6 mg/dL	CF = mg x 8.8 = µmol Based on normal ranges: ≤0.6 mg/dL (0-1 year), 0.5 to 1.5 mg/dL (1 to 16/18 years)
	6 years to <12 years old (Children)	≥90 µmol/L or 1.1mg/dL	
	12 years to 16/18 years old (Adolsecents)	≥132µmol/L or 1.5mg/dL	
Creatinine Clearance	All age ranges	50 % of normal <60 ml/min/1.73m2 (After 1 year old)	Based on GFR Bedside Schwartz Formula Based on normal ranges: 20 to 50 (<8 days), 25 to 80 (8 days to 1 month), 30 to 90 (1-6 months), 40 to 115 (6-12 months), 60 to 190 (12-23 months), 90 to 165 (2-12 years), 80-120 (After 12 years)
Uric Acid	All age ranges	≤2.0 mg/dL or 119 µmol/L ≥8.0 mg/dL or 476 µmol/L	CF = mg x 5.95 = µmol Based on normal ranges: 2.4 to 6.4 mg/dL
Blood Urea Nitrogen (BUN)	Birth/0 to 27 days old (Neonates)	≥4.3 mmol/L or 12 mg/dl	CF = g x 16.66 = mmol Based on normal ranges: 3 to 12 mg/dL (NN; 5 to 18 mg/dL (other classes of age)
	28 days/1 month to 16/18 years old (Infants, Children, Adolescents)	≥6.4 mmol/L or 18 mg/dl	
Chloride	All age ranges	≤80 mmol/L or 80 mEq/L ≥115 mmol/L or 115 mEq/L	CF = 1 Based on normal range: 98 to 106
Sodium	All age ranges	≤129 mmol/L or 129 mEq/L ≥150 mmol/L or 150 mEq/L	CF = 1

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
			Based on normal range : 134 to 146
Potassium	Birth/0 to 27 days old (Neonates)	≤3.0 mmol/L or 3.0 mEq/L ≥7.0 mmol/L or 7.0 mEq/L	CF = 1 Based on normal ranges: 3.0 to 7.0 (NN); 3.5 to 6.0 (Infants); 3.5 to 5.0 (>Infants)
	28 days/1 month to 23 months old (Infants)	≤3.5 mmol/L or 3.5 mEq/L ≥6.0 mmol/L or 6.0 mEq/L	
	24 months/2 years to 16/18 years old (Children, Adolescents)	≤3.5 mmol/L or 3.5 mEq/L ≥5.5 mmol/L or 5.5 mEq/L	
Bicarbonate	All age ranges	≤16 mmol/L or 16 mEq/L ≥30 mmol/L or 30 mEq/L	CF = 1 Based on normal range: 18 to 26
Calcium total	All age ranges	≤2.0 mmol/L or 8.0 mg/dL ≥2.9 mmol/L or 11.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 8.4 to 10.9 mg/dL
Calcium ionized	All age ranges	≤1.0 mmol/L or 4.0 mg/dL ≥1.4 mmol/L or 5.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 4.0 to 5.1 mg/dL
Total Cholesterol	All age ranges	≥6.20 mmol/L or 240 mg/dL	CF = g x 2.58 = mmol Based on normal ranges: 45 to 182 mg/dL (1-3 years), 109 to 189 mg/dL (4-6 years), 126 to 191 mg/dL (Boys 6-9 years), 122 to 209 mg/dL (Girls 6-9 years), 130 to 204 mg/dL (Boys 10-14 years), 124-217 mg/dL (Girls 10-14 years), 114 to 198 mg/dL (Boys 15-19 years), 125 to 212 mg/dL (Girls 14-19 years)
Triglycerides	All age ranges	≥4.0 mmol/L or 350 mg/dL	After >12 hours of fast) CF = g x 1.14 = mmol Based on normal ranges: 30 to 86 mg/dL (Boys 0-5 years), 32 to 99 mg/dL (Girls 0-5 years), 31-108 mg/dL (Boys 6-11 years), 35 to 114

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
			mg/dL (Girls 6-11 years), 36 to 138 mg/dL (Boys 12-15 years), 43 to 138 mg/dL (Girls 12-15 years), 40 to 163 mg/dL (Boys 16-19 years), 40-128 mg/dL (Girls 16-19 years)
Lipasemia	All age ranges	≥2 ULN	Based on normal ranges: 3 to32 U/L (1-18 years)
Amylasemia	All age ranges	≥2 ULN	Based on normal ranges: 10 to 30 U/L (NN), 10 to 45 U/L (1-18 years)
Glucose	All age ranges	Hypoglycaemia <2.7 mmol/L or 50 mg/dL Hyperglycaemia ≥7 mmol/L or 120 mg/dL (fasted after >12 hours of fast); ≥10.0 mmol/L or 180 mg/dL (unfasted)	CF = g x 5.55 = mmol Based on normal ranges: 50 to 90 mg/dL (NN), 60 to 100 mg/dL (Child)
CRP	All age ranges	>2 ULN or >10 mg/L (if ULN not provided)	Based on normal ranges: <6 mg/L
Hematology			Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2006 ; Division of Microbiology and Infectious Diseases Pediatric Toxicity Tables, 2007 ; Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2004; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Family Practice Notebook, LLC, 2012; Tietz NW et al. Clinical Guide to Laboratory Testing, 3rd edition 1995
WBC	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4,000 /mm3 >25.0 GIGA/L or 25,000 /mm3	To be used if no differential count available Based on normal ranges: 9,000 to 30,000 /mm3 (birth), 9,400 to 38,000 /mm3 (0-1
	28 days/1 month to 23 months old (Infants)	<4.0 GIGA/L or 4,000 /mm3 >20.0 GIGA/L or 20,000 /mm3	
	24 months/2 years to <6 years old (Children)	<3.0 GIGA/L or 3,000 /mm3 >16.0 GIGA/L or 16,000 /mm3	
	6 to <12 years old (Children)	<5.0 GIGA/L or 5,000 /mm3	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
		>17.0 GIGA/L or 17,000 /mm3	day), 5,000 to 21,000 /mm3 (1 day-1 month), 6,000 to 17,500 /mm3 (1 month-2 years), 5,000 to 17,000 /mm3 (2-6 years), 4,500 to 15,500 /mm3 (6-11 years), 4,500 to 13,500 /mm3 (11-18 years)
	12 to 16/18 years old (Adolescents)	<4,5 GIGA/L or 5,000 /mm3 >13.5 GIGA/L or 17,000 /mm3	
Lymphocytes (ALC)	Birth/0 to 27 days old (Neonates)	<1.2 GIGA/L or 1,200 /mm3 >17.0 GIGA/L or 17,000 /mm3	Based on normal ranges: 2,000 to 11,500 /mm3 (0-1 days), 2,000 to 17,000 /mm3 (2 days-1 month), 3,000 to 13,500 /mm3 (1 month-2 years), 1,500 to 9,500 /mm3 (2-6 years), 1,500 to 8,000 /mm3 (6-10 years), 1,200 to 5,200 /mm3 (10-18 years)
	28 days/1 month to 23 months old (Infants)	<2.0 GIGA/L or 2,000 /mm3 >13.5 GIGA/L or 13,500 /mm3	
	24 months/2 years to <6 years old (Children)	<1.0 GIGA/L or 1,000 /mm3 >9.5 GIGA/L or 9,500 /mm3	
	6 to <12 years old (Children)	<1.0 GIGA/L or 1,000 /mm3 >8.0 GIGA/L or 8,000 /mm3	
	12 to 16/18 years old (Adolescents)	<0.6 GIGA/L or 600 /mm3 >6.0 GIGA/L or 6,000 /mm3	
Absolute Neutrophil Count (ANC)	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4,000 /mm3 (1 day old) <1.5 GIGA/L or 1,500 /mm3 (2-7 days old) <1.25 GIGA/L or 1,250 /mm3 (>7 day-1 month old) > 1 ULN	Based on normal ranges: 5,000 to 28,000 /mm3 (0-1 day), 1,000 to 10,000 (1 day-1 month), 1,000 to 8,500 (1-12 months), 1,500 to 8,500 (1 to 6 years), 1,500 to 8,000 (6 to 10 years), 1;800 to 8,000 (10 to 18 years)
	28 days/1 month to 23 months old (Infants)	<1.0 GIGA/L or 1,000/mm3 (1-3 months) <1.2 GIGA/L or 1,200 /mm3 (3-24 months) > 1 ULN	
	24 months/2 years to <6 years old (Children)	<1.2 GIGA/L or 1,200 /mm3 > 1 ULN	
	6 to <12 years old (Children)	<1.2 GIGA/L or 1,200 /mm3 > 1 ULN	
	12 to 16/18 years old (Adolescents)	<1.2 GIGA/L or 1,200 /mm3 > 1 ULN	
Eosinophils	All age ranges	>0.5 GIGA/L or 500 /mm3 Or >ULN if ULN >0.5 GIGA/L or 500 /mm3	Based on normal ranges: 0 to 500 /mm3 (0-1 month), 0 to 300 /mm3 (1 month-18 years)
Hemoglobin	Birth/0 to 27 days old (Neonates)	< 86 mmol/L or 12.0 g/dL or any decrease $\geq$ 0.31 mmol/L or 2 g/dL	CF = g x 1.55 = mmol Based on normal ranges: 15 to 20 g/dL (0-3 days), 12.5 to 18.5 g/dL (1-2 weeks), 10.0 to 13.0 g/dL (1-6 months), 10.5 to 13.0 g/dL (7 months-2 years), 11.5 to 13.0 g/dL (2-5 years), 11.5 to 14.5 (5-8 years), 12.0 to 15.2 g/dL (13-18 years)
	28 days/1 month to 23 months old (Infants)	< 1.40 mmol/L or 9.0 g/dL or any decrease $\geq$ 0.31 mmol/L or 2 g/dL	
	24 months/2 years to <16/18 years old (Children, Adolescents)	< 1.55 mmol/L or10.0 g/dL or any decrease $\geq$ 0.31 mmol/L or 2 g/dL	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For Studies in Children

Parameter	Age range	PCSA	Comments
Hematocrit	Birth/0 to 27 days old (Neonates)	< 0.39 l/l or 40 % > 0.61 l/l or 47 %	CF = % x 0.01 = l/l Based on normal ranges: 45 to 61 % (0-3 days), 39 to 57 % (1-2 weeks), 29 to 42 % (1-6 months), 33 to 38 % (7 months-2 years), 34 to 39 % (2-5 years), 35 to 42 % (5-8 years); 36 to 47 % (13-18 years)
	28 days/1 month to 23 months old (Infants)	< 0.29 l/l or 29 % > 0.42 l/l or 42 %	
	24 months/2 years to <16/18 years old (Adolescents)	< 0.32 l/l or 32 % > 0.47 l/l or 47 %	
Platelets	All age ranges	<100 GIGA/L or 100,000 /mm3 > 700 GIGA/L or 700,000 /mm3	Based on normal ranges: 250,000 to 450,000 /mm3 (NN); 300,000 to 700,000 /mm3 (1-6 months), 250,000 to 600,00 /mm3 (7 months-2 years), 250,000 to 550,000 /mm3 (2-12 years), 150,000 to 450,000 /mm3 (13-18 years)
Urinalysis			Patel HP, Pediatr Clin N Am, 2006
Ketonuria	All age ranges	Presence	Semi-quantitative methods
Glycosuria	All age ranges	Presence	Semi-quantitative methods
Hematuria	All age ranges	$\geq$ 1+	Semi-quantitative methods
Proteinuria	All age ranges	$\geq$ 1+	Semi-quantitative methods

Appendix B Visit Windows Based on Day Ranges for Laboratory values, Vital Signs, ADA, and PK measurements

Measurements of PK and ADA will be mapped to each visit/time point based on Table 1; Labs and vital signs will be mapped to each visit/time point based on Table 2. Below are the rules for the lab tests that are not included in Table 2:

- Pregnancy test results will be summarized at baseline and post-treatment, where the baseline will be defined based on all the pregnancy tests (serum and urine) performed prior to the first IMP; and post-treatment value will be based on all the pregnancy tests performed post first IMP. The value is positive if at least one of the tests is positive.
- Rheumatoid factor (RF) and Urinalysis will only be measured during the screening period. Only the value at baseline will be summarized.

Table 1 - Day Range for Each Defined Visit/Time for PK and ADA

Week	Target day[a]	PK	ADA
W0	1	Day≤1	Day≤1
D3	3	2≤Day<4	
D5	5	4≤Day<7	
D8	8	7≤Day<10	
D12	12	10≤Day<14	
W2	15	14≤Day<22	
W4	29	22≤Day<43	
W8	57	43≤Day<71	
W12	85	71≤Day<127	2≤Day<127
W24	169	127≤Day<253	127≤Day<253
W48	337	253≤Day<421	253≤Day<421
W72	505	421≤Day<589	421≤Day<589
W96	673	589≤Day<757	589≤Day<757
W120	840	757≤Day<967	757≤Day<967
W156	1092	Day[b]≥967	Day[b]≥967
EOT+2	n.a.	Day[c]≥2	n.a.
Follow-up	n.a.	Day[d]≥2	Day[d]≥2

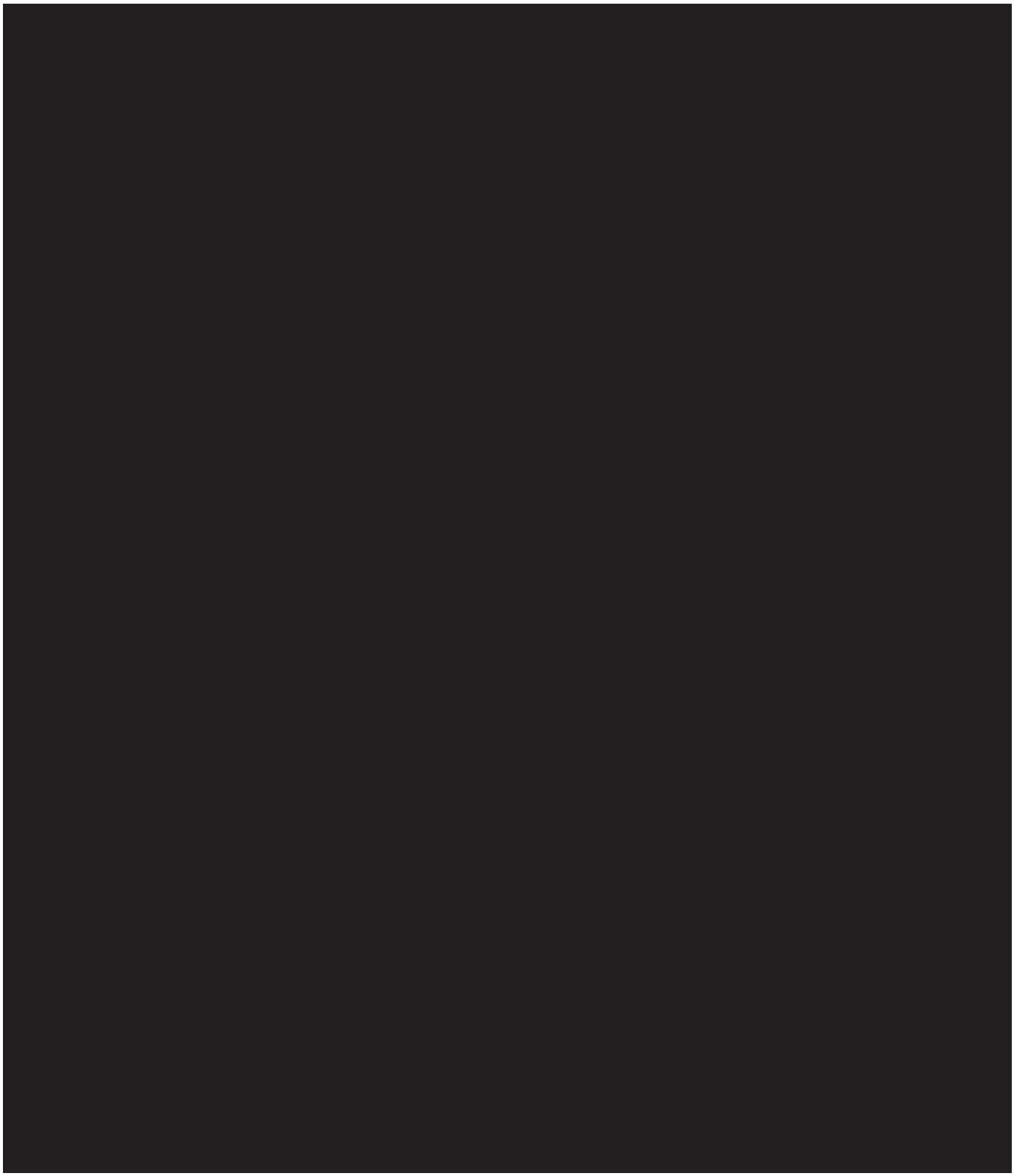
Week	Target day[a]	PK	ADA

a Based on days relative to the reference day (ie, the date of first dose of sarilumab).
b Excluding the measurements at the end of study follow-up visit (ie, per protocol, 6 weeks after end of treatment visit) and at V88 for PK.
c Only applicable to patients who d/c the study during the core treatment phase or not going to enter the extension phase - includes only the measurement(s) at V88 (ie, per protocol, 2 weeks after end of treatment visit).
d Includes only the measurement(s) at the end of study follow-up visit V28 (ie, per protocol, 6 weeks after end of treatment visit).

Table 2 - Day Range for Each Defined Visit/Time for Lab and Vital Signs

Week	Target day[a]	[redacted]	[redacted])	lipids	ANA/Anti-ds DNA antibody	Vital signs (Temperature [pcJIA], HR, BP)	Vital signs (Weight)	Vital signs (Height)
W0	1			Day≤1	Day≤1	Day≤1	Day≤1	Day≤1
D3	3							
D5	5							
D8	8							
D12	12							
W2	15							
W4	29			2≤Day<57		2≤Day<43		
W6	43							
W8	57					43≤Day<71		
W10	71							
W12	85			57≤Day<127	2≤Day<127	71≤Day<99	2≤Day<99	2≤Day<127
W16	113					99≤Day<127	99≤Day<127	
W20	141					127≤Day<155	127≤Day<155	
W24	169			127≤Day<253	127≤Day<253	155≤Day<196	155≤Day<196	127≤Day<253
W32	225					196≤Day<253	196≤Day<253	
W40	253					253≤Day<309	253≤Day<309	
W48	337			253≤Day<421	253≤Day<421	309≤Day<379	309≤Day<379	253≤Day<421
W60	421					379≤Day<463	379≤Day<463	
W72	505			421≤Day<589	421≤Day<589	463≤Day<547	463≤Day<547	421≤Day<589
W84	589					547≤Day<631	547≤Day<631	
W96	673			589≤Day<757	589≤Day<757	631≤Day<715	631≤Day<715	589≤Day<757
W108	756					715≤Day<799	715≤Day<799	
W120	840			757≤Day<925	757≤Day<925	799≤Day<883	799≤Day<883	757≤Day<925
W132	924					883≤Day<966	883≤Day<966	
W144	1008			925≤Day<1051	925≤Day<1051	966≤Day<1051	966≤Day<1051	925≤Day<1051
W156	1092			Day≥1051	Day≥1051	Day[b]≥1051	Day[b]≥1051	Day≥1051
Follow-up	n.a.			n.a.	n.a.	Day[c]≥2	Day[c]≥2	n.a.

a Based on days relative to the date of first dose of sarilumab.
b Excluding the measurements at the end of study follow-up visit (ie, per protocol, 6 weeks after end of treatment visit).
c Includes only the measurement(s) at the end of study follow-up visit V28 (ie, per protocol, 6 weeks after end of treatment visit).



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