# STATISTICAL ANALYSIS PLAN

**An adaptive phase 3, randomized, double-blind, placebo-controlled study assessing efficacy and safety of sarilumab for hospitalized patients with COVID-19**

**SAR153191-EFC16844**

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ADA | Anti-drug antibody |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| ARDS | Acute respiratory distress syndrome |
| AST | Aspartate aminotransferase |
| BUN | Blood urea nitrogen |
| CDC | Center for Disease Control |
| COVID-19 | Coronavirus Disease 2019 |
| CPK | Creatine phosphokinase |
| CRF | Case report form (electronic or paper) |
| CRO | Contract research organization |
| CRP | C-reactive protein |
| CRS | Cytokine release syndrome |
| ECG | Electrocardiogram |
| ECMO | Extracorporeal membrane oxygenation |
| EDC | Electronic data capture |
| FDA | Food and Drug Administration |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| ICU | Intensive care unit |
| IL-6 | Interleukin 6 |
| IMP | investigational medicinal product |
| IRB | Institutional Review Board |
| IV | Intravenous |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Events |
| NEWS2 | National Early Warning Score2 |
| NP | Nasopharyngeal |
| PK | Pharmacokinetic(s) |
| RBC | Red blood cell |
| SAE | Serious adverse event |
| SAF | Safety analysis set |
| SAP | Statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SAS | Statistical Analysis System |
| SC | Subcutaneous |
| SOC | System organ class |
| sIL-6R | Soluble interleukin-6 receptor |
| SpO$_2$ | Peripheral capillary oxygen saturation |
| SUSAR | Suspected unexpected serious adverse reaction |
| TEAE | Treatment-emergent adverse event |
| WBC | White blood cell |
| WHO | World Health Organization |

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# 1 OVERVIEW AND INVESTIGATIONAL PLAN

## 1.1 STUDY DESIGN AND RANDOMIZATION

This study is a randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of sarilumab in hospitalized adults with severe or critical COVID-19. The study will be conducted in Europe and other countries except in the United States (US) in up to 100 sites.

Approximately 400 patients will be randomized via interactive response technology (IRT) in a 2:2:1 allocation ratio to sarilumab 400 mg IV, sarilumab 200 mg IV, or placebo. Randomization will be stratified by severity of illness (severe, critical) and use of systemic corticosteroids (yes, no), and balanced by region. All patients will receive a single dose of study drug on Day 1. Patients may receive a second dose with study drug (based on the original treatment group assigned) 24 to 48 hours after the first dose, if they meet prespecified criteria in protocol.

Severity of illness categories:

- Severe disease:

  - Requires supplemental oxygen administration by nasal cannula, simple face mask, or other similar oxygen delivery device

- Critical disease:

  - Requires supplemental oxygen requiring delivered by non-rebreather mask or high flow nasal cannula, or

  - Use of invasive or non-invasive ventilation, or

  - Requiring treatment in an intensive care unit.

Patients will be assessed daily while hospitalized. Patients discharged from the hospital prior to Day 29 will be contacted with a follow-up phone call on Day 29 to assess status and occurrence of re-admission to a hospital. Patients will undergo a series of efficacy, safety and laboratory assessments while in the hospital. Serum IL-6 and other markers will be collected and analyzed in a central laboratory. Nasopharyngeal (NP) samples to monitor viral infection and blood samples may be obtained on Day 1 (pre-dose), 4, 7, 15,29 (or up until the day of discharge if the patient is discharged from the hospital before Day 29). An individual patient will complete the study approximately 60 days from screening to follow-up on day 60 ±7 days. Patients will not be required to return to the hospital once discharged.

## 1.2 OBJECTIVES

### 1.2.1 Primary objective

To evaluate the clinical efficacy of sarilumab relative to the control arm in adult patients hospitalized with severe or critical COVID-19.

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### 1.2.2 Secondary objectives

- Evaluate the 28-day survival rate

- Evaluate the clinical efficacy of sarilumab compared to the control arm by clinical severity

- Evaluate changes in the National Early Warning Score 2 (NEWS2)

- Evaluate the duration of predefined symptoms and signs (if applicable)

- Evaluate the duration of supplemental oxygen dependency (if applicable)

- Evaluate the incidence of new mechanical ventilation use during the study

- Evaluate the duration of new mechanical ventilation use during the Study

- Evaluate the proportion of patients requiring rescue medication during the 28-day period

- Evaluate need for admission into intensive care unit (ICU)

- Evaluate duration of hospitalization (days)

- The secondary safety objectives of the study are to evaluate the safety of sarilumab through hospitalization (up to Day 29 if patient is still hospitalized) compared to the control arm as assessed by incidence of:

    - Serious adverse events (SAEs)

    - Major or opportunistic bacterial or fungal infections in patients with grade 4 neutropenia

    - Grade ≥2 infusion related reactions

    - Grade ≥2 hypersensitivity reactions

    - Increase in alanine transaminase (ALT) ≥3X ULN (for patients with normal baseline) or >3X ULN and at least 2-fold increase from baseline value (for patients with abnormal baseline)

    - Major or opportunistic bacterial or fungal infections


### 1.3    DETERMINATION OF SAMPLE SIZE

The sample size calculations are performed based on the primary endpoint, the time to improvement of 2 points in clinical status assessment from baseline using the 7-point ordinal scale.

Assuming that accrual duration is 3 months (~90 days) with each patient followed for a period of at least 29 days, the proportions of patients with two points improvement from baseline in clinical status assessment at Day 15 are 45% and 70% for placebo and sarilumab, respectively, a total sample size of approximately 400 patients with a 2:2:1 randomization ratio provides at least 90% power for pairwise comparisons between each sarilumab dose (400 mg IV or 200 mg IV; n~160 each) and placebo (n~80), using a log-rank test of superiority at a two-sided significance level of 0.05. Sample size calculation was performed using PASS 14.

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## 1.4 STUDY PLAN

The schedule of activities can be found in Section 1.3 of the study protocol. The graphical study design is provided in Figure 1.

**Figure 1 - Graphical study design**
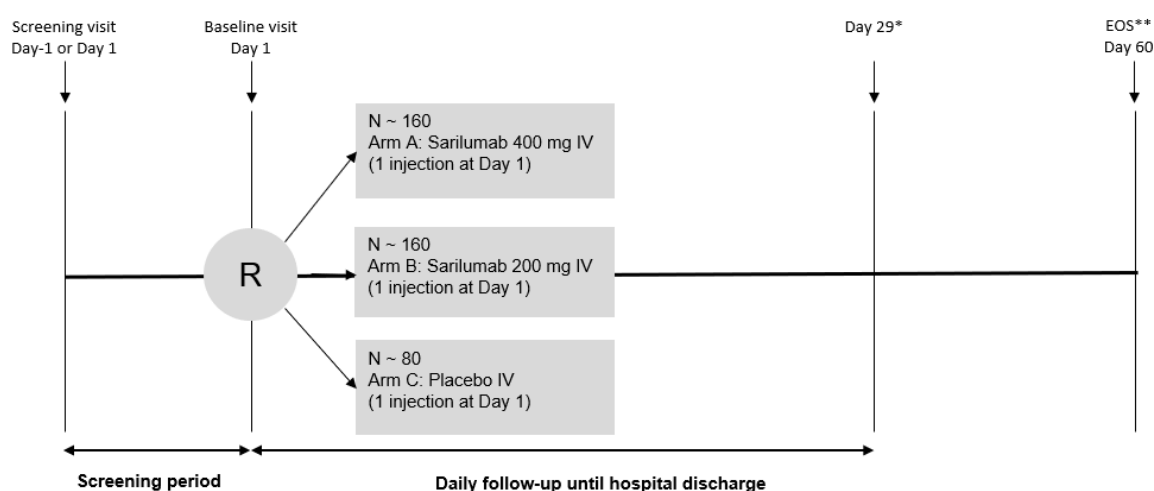


\* If the patients has been discharged from the hospital before Day 29, the study site staff will contact the patient for a follow-up phone call
\*\* The EOS will be on Day 60 or day of death, whichever comes first. If the patient has been discharged from the hospital before Day 60, the study site staff will contact the patient for a follow-up phone call

R: Randomized; EOS: End of study; IV: intravenous; N: number

## 1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The original protocol (dated: 18 March 2020) was updated to amendment 01 (dated: 26 March 2020), and amendment 02 (dated: 8 April 2020). The Table 1 below gives the timing, rationale, and key details of major changes to the protocol statistical section.

**Table 1 – Protocol amendment statistical changes**

| Amendment Number | Date Approved | Rational | Description of statistical changes |
|---|---|---|---|
| 01 | 26-Mar-2020 | To provide power calculation for both phase 2 and phase 3 primary endpoints | • The power calculation for phase 3 primary endpoint was added |

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| | | | |
|---|---|---|---|
| | | To specify the multiplicity control method | • Details of the multiplicity control method were added |
| | | To specify interim analysis | • A planed analysis at the end of Phase 2 was added in Interim Analysis section |
| 02 | 08-Apr-2020 | Study design was changed from adaptive phase 2/3 to adaptive phase 3, and new primary and key secondary endpoints were specified | • Updated the sample size/power calculation based on the new primary endpoint,<br>• Change total number of patients needed from 300 to 400 in sample size section<br>• Updated the analyses of the primary and key secondary endpoints<br>• Multiplicity control method was revised<br>• Interim analysis at ~50% of total planned number of patients (~200) was added to replace the end of phase 2 analysis |
| 03 | 29-Apr-2020 | To clarify the scope of adaptations the Sponsor may make based on the interim analysis results | • Remove requirement that the interim analysis requires data up to Day 15<br>• Specify the type of modifications that the Sponsor may make based on the interim analysis results |

## 1.6    STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan and/or protocol.

| SAP version Number | Date Approved | Rational | Description of statistical changes |
|---|---|---|---|
| 1 | 30-Apr-2020 | | Original SAP |
| 2 | 05-May-2020 | Change the interim analysis timing and clarify the scope of adaptations the Sponsor may make based on the interim analysis results according to Protocol Amendment 3 | • Remove requirement that the interim analysis requires data up to Day 15 in section 3 Interim analysis.<br>• Specify the type of modifications that the Sponsor may make based on the interim analysis results in section 3 Interim analysis. |

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# 2    STATISTICAL AND ANALYTICAL PROCEDURES

## 2.1    ANALYSIS ENDPOINTS

### 2.1.1    Demographic and baseline characteristics

In general, the baseline value is defined as the last available value prior to the first dose of investigational medicinal product (IMP) or the last available value on or before the date of randomization for patients who were randomized but never exposed to IMP, unless otherwise specified.

*Demographic characteristics*

The following demographic characteristics will be summarized separately by treatment and overall:

- Age at screening (years)
- Age group ($\geq$18 and <64, $\geq$65 and <84, $\geq$85 years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not Reported, Unknown). Note: Japanese will be included in Asian
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Baseline height (cm)
- Baseline weight (kg)
- Baseline weight category (<50, 50 to <100, $\geq$100 kg)
- Baseline body mass index (BMI, kg/m$^2$) (<18.5, 18.5 to <25, 25 to <30, $\geq$30)

*Disease characteristics at baseline*

The following baseline disease characteristics will be summarized:

- Severity of illness (per IRT) (Severe, Critical)
- Severity of illness (as recorded on CRFs) (Severe, Critical)
- Systemic corticosteroids use (per IRT) (Yes, No)
- Systemic corticosteroids use (as recorded on CRFs) (Yes, No)
- Clinical status using 7-point ordinal scale
- Body temperature prior to dosing (ºC) (defined as the highest temperature at any time prior to first dose)
- Fever (Yes, No)

- SARS-CoV-2 virus detected (Positive, Negative)
- CRP level

The other baseline disease characteristic includes

- Pneumonia status

  – Pneumonia present based on historical chest X-Ray, CT scan or MRI or lung auscultation (Yes, No)

  – Signs and symptoms: Fever, Cough, Dyspnea (Yes, No)

  – Time from dyspnea onset to baseline

  – Type of oxygen delivery device (Nasal cannula, simple face mask, non-rebreather face mask, high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, other)

  – Use of extracorporeal life support life support (Yes, No)

  – Use of renal replacement therapy (Yes, No)

  – Use of vasopressors (Yes, No)

- Oxygen administration and oxygenation

  – Supplemental Oxygen or mechanical ventilation used (Yes, No)

  – Oxygen flow rate (L/min)

  – Oxygen saturation (SpO2 %) (range is 0% to 100%)

  – FiO2 (fraction of inspired oxygen) (range is 0.0 to 1.0) – see Section 2.5.2 for derivations

  – SpO2/FiO2 ratio – see Section 2.5.2 for derivations

- Hospitalization and ICU admission

  – Duration of hospitalization prior to dosing

  – ICU required (Yes, No)

    – If yes, ICU admitted (Yes, No)

  – Duration of ICU admission prior to dosing

### *Medical history*

Medical history, concomitant diseases or past surgeries or surgical history are recorded.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

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

### 2.1.2 Concomitant medications

All medications taken from screening to day 60 (or until day of discharge from hospital if before Day 60) captured include:

- Corticosteroids, NSAIDs, and any other anti-pyretics

- Antivirals (eg, remdesivir), antifungals, antibacterials, antimycobacterials, antiprotozoans, antihelminthics, antimalarials (eg, chloroquine and hydroxychloroquine)

- Interferon beta and convalescent serum.

- Angiotensin converting enzyme and Angiotensin receptor blocking

- Agents that may affect the CYP450 substrate.

- Any rescue medication that is used during the course of the study.

All medications will be coded using the World Health Organization – Drug Dictionary (WHO-DD) version currently in effect at Sanofi at the time of database lock.

Concomitant medications are any treatments received by the patient concomitantly to the IMP, during the treatment-emergent period (as defined in the observation period in Section 2.1.4).

During the study, for patients requiring rescue therapy as per the judgement of the study physician, additional medications may be utilized. Rescue medications are defined as the immunosuppressive therapies (described in the exclusion criteria E03 and E04).

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

### 2.1.3 Efficacy endpoints

#### 2.1.3.1 Primary efficacy endpoint(s)

The primary endpoint is the time to improvement of 2 points in clinical status assessment from baseline using the 7-point ordinal scale.

The 7-point ordinal scale is an assessment of the clinical status. The scale is as follows:

- 1. Death;

- 2. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);

- 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;

- 4. Hospitalized, requiring supplemental oxygen;

- 5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);

- 6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care

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- 7. Not hospitalized

### 2.1.3.2  Secondary efficacy endpoint(s)

The key secondary endpoint is the proportion of patients alive at Day 29.

Other secondary endpoints are:

1. Proportion of patients with one-point improvement from baseline in clinical status assessment at days 4, 7, 15, 21, 29 using the 7-point ordinal scale

2. Mean change in 7-point ordinal scale from baseline to days 4, 7, 15, 21, 29 (or until discharge)

3. Time to resolution of fever defined as body temperature (≤36.6°C [axilla], or ≤37.2 °C [oral], or ≤37.8°C [rectal or tympanic]) for at least 48 hours without antipyretics or until discharge, whichever is sooner

4. Time to resolution of fever (as defined above) and improvement in oxygenation (as defined below)

5. Days with fever (>37.4°C [axilla], or >38.0 °C [oral], or >38.4°C [rectal or tympanic]) based on maximum value observed during a 24-hour period.

6. Time to change in National Early Waring Score 2 (NEWS2) from baseline

7. Time to NEWS2 of <2 and maintained for 24 hours

8. Mean change from baseline to Day 4, 7, 15, 21, 29 in NEWS2

9. Time to improvement in oxygenation (SpO2/FiO2 of 50 or greater) compared to the nadir for at least 48 hours, or until discharge, whichever is sooner

10. Alive off supplemental oxygen at Day 29

11. Days of hypoxemia (SpO2 <93% on room air, or requiring supplemental oxygen, or mechanical ventilatory support)

12. Days of supplemental oxygen use

13. Days of resting respiratory rate >24 breaths/min (maximum value if recorded at more than once a day)

14. Time to saturation ≥94% on room air

15. Ventilator free days in the first 28 days (to Day 29)

16. Initiation of mechanical ventilation, non-invasive ventilation, or use of high flow nasal cannula (for those not requiring these interventions at baseline)

17. Proportion of patients requiring rescue medications during the 28-day period

18. ICU status (among those not in an ICU at baseline, record if transferred to the ICU or the need to transfer to the ICU [if the ICU is not available])

19. Days of hospitalization among survivors

### 2.1.4  Safety endpoints

The safety analysis will be based on the reported adverse events (AEs), serious AEs (SAEs) and adverse events of special interest (AESIs). Other safety information, such as clinical laboratory data, and vital signs will also be assessed as applicable.

*Observation period*

There are 3 parts in the observation period:

- **Screening** period is defined as the time from the signed informed consent date up to the time prior to first dose of IMP.

- **On-treatment** period is defined as the day from the first dose of the IMP to the last dose of the IMP + 60 days.

- **P**ost-treatment period is defined as the time after the last dose of IMP +60 days.

The treatment-emergent adverse event (TEAE) period is the **on-treatment** period.

The on-study observation period is defined as the time from start of treatment until the end of the study (defined as last protocol planned visit or the resolution/stabilization of all serious adverse events and AESI).

### 2.1.4.1  Adverse events variables

*Adverse event observation period*

- Pre-treatment AEs are AEs that developed or worsened or became serious from the signed informed consent date up to first administration of IMP

- TEAEs are AEs that developed or worsened or became serious during the TEAE period

- Post-treatment AEs are AEs that developed or worsened or became serious during the post-treatment period

All AEs (including SAEs and AESIs) will be coded to a "LLT", "PT", "HLT", "HLGT", and associated primary "SOC" using the version of MedDRA currently in effect at Sanofi at the time of database lock.

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

*Adverse events of special interest (AESI*; serious and nonserious) include the following:

- Grade ≥2 infusion related reactions (Infusion related reactions are defined as any signs or symptoms experienced by patients who receive IMP within 24 hours of the start of infusion)

- Grade ≥2 hypersensitivity reactions

- Grade 4 neutropenia (ANC<500/mm3)

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- Grade 4 neutropenia with concurrent invasive infection (ANC<500/mm3)

- Increase in alanine transaminase (ALT) ≥3X ULN (for patients with normal baseline) or >3X ULN AND at least 2-fold increase from baseline value (for patients with abnormal baseline)

- Invasive bacterial or fungal infections of clinical significance with confirmed diagnosis based on the Investigator's assessment with appropriate diagnostic workups and consultations

- Symptomatic overdose (serious or nonserious) with IMP

  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as an increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.

AESIs will be flagged in the database using search criteria. All AEs captured on the general AE form, the ALT increase form, infusion reaction symptoms form, and the infection event form will be searched. The list of search criteria is provided in Appendix C.

### 2.1.4.2 Deaths

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

- Death on-study: deaths occurring during the on-study period
- Death post-study: deaths occurring after the end of study

### 2.1.4.3 Laboratory safety variables

Clinical laboratory data will include hematology, clinical chemistry, urinalysis and infection tests. Clinical laboratory values will be converted to standard international units; international units will be used in all listings and tables.

Hematology and chemistry data will be collected at screening, baseline, days 2 or 3 (only for patients with second dose), 4, 7, 15, 21 and 29 or discharge. The laboratory parameters will be classified as follows:

- Hematology

  - **Red blood cells and platelets and coagulation**: hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, and RBC indices (MCV, MCH, %Reticulocytes).

  - **White blood cells:** white blood cell (WBC) count and WBC differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils)

- Clinical chemistry

  - **Metabolism:** total proteins, CRP, and glucose (fasting or non-fasting)

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- **Electrolytes**: sodium, potassium, and calcium.

- **Renal function**: creatinine, and blood urea nitrogen (BUN).

- **Liver function**: alanine aminotransferase (ALT)/SGPT, aspartate aminotransferase (AST)/SGOT, alkaline phosphatase (ALP), total and direct bilirubin

- Ferritin

- D-dimer

Urine samples will be collected as follows:

- **Urinalysis** - dipstick: pH, blood, glucose, protein, ketones, nitrates, leukocyte esterase, and bilirubin.

- Specific gravity

Infection tests include:

- Bacterial and fungal blood culture

### 2.1.4.4  Vital signs variables

Vital signs variables include heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure (daily until discharge). It also includes height and weight at screening only.

### 2.1.4.5  Physical Examination

A targeted physical examination including lung auscultation and assessment of consciousness will be performed at time points specified in protocol.

### 2.1.4.6  Electrocardiogram variables

A standard 12-lead ECG will be performed optionally at time points specified in protocol. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (identify QTcB or QTcF) intervals will be recorded in the eCRF.

### 2.1.4.7  Anti-sarilumab antibodies

Samples analyzed in the antidrug antibody (ADA) assay will be categorized as either positive or negative.

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

### 2.1.5 Pharmacokinetics variables

Sarilumab concentration will be collected at Day 1, 2 or 3 (only for patients with second dose), Day 4, 7, 15, 21 and 29 or early discharge.

### 2.1.6 Biomarker and other variables

Measurement of SARS-CoV-2 (Blood sample) or SARS-CoV-2 (NP swab), and the concentration of CRP, IL-6 and sIL-6R will be collected by schedule specified in protocol.

### 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 any patients who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all patients with a signed informed consent form and randomized, regardless of whether the study drug was used.

The total number of patients for each one of the following categories will be presented in the clinical study report (CSR) using a summary table:

- Screened patients
- Screen failure patients and reasons for screen failure
- Randomized patients
- Randomized but not treated patients
- Randomized and treated participants
- Patients who reached Day 29 (while still hospitalized)
- Patients who did not reach Day 29 and the reasons

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- Patients who completed the follow-up (Day 60)

- Patients who did not complete follow-up (Day 60) and main reason for not completing follow-up.

In addition, the number (%) of patients screened, randomized, reached Day 29 and completed follow-up to Day 60 will be provided by country and site.

All critical or major deviations potentially impacting efficacy analyses, randomization and drug dispensing irregularities and other major/critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Additionally, the analysis populations for safety, efficacy, per protocol, and PK/PD/Immunogenicity will be summarized in a table by patient counts based on the randomized populations (see definitions in Section 2.3).

- ITT population (Randomized population)

- Efficacy population (modified intention-to-treat (mITT))

- Per protocol population (PPS)

- Safety population

- PK population

- ADA population

## 2.2.1 Randomization and drug dispensing irregularities

Randomization will be monitored throughout the study and reviewed on an ongoing basis. Any drug-dispensed wrongly will be identified and documented by manual deviation.

All randomization 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 randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

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

**Table 2 - Randomization and Drug Allocation Irregularities**

| Randomization and Drug Allocation Irregularities |
|---|
| *Erroneous treatment dispensation (will be identified by manual deviation)* |
| *Kit not available* |
| *Randomization by error* |
| *Subject randomized twice* |
| *Forced randomization* |

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## 2.3    ANALYSIS POPULATIONS

Enrolled population are all patients who sign the inform consent form (ICF).

Randomized population are all randomized patients regardless of IMP was administered.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

### 2.3.1   Efficacy populations

#### 2.3.1.1   Intent–to-treat/Modified intent-to-treat population

The intent-to-treat population (ITT) is the randomized population analyzed according to the treatment group allocated by randomization.

The modified intention-to-treat (mITT) population includes all randomized patients who received at least one dose of the study drug. Analysis of the mITT population will be done according to the initial treatment assigned to the patient (as randomized). The mITT population will be the primary population for analysis of primary and secondary efficacy endpoints, as well as for data including (but not limited to) demographics and baseline characteristics.

#### 2.3.1.2   Per-protocol population

The Per Protocol population set (PPS) includes all ITT patients who did not have any relevant major protocol deviations, eg, patients who are randomized and treated, but do not have laboratory-confirmed SARS-CoV-2 infection will be excluded from PPS. The final determination of the exclusion of patients from the PPS will be made prior to the primary database lock. Analysis of the PPS will be done according to the treatment the patient received. The PPS will be used as sensitivity analysis for the primary efficacy endpoint.

### 2.3.2   Safety population

The safety population includes all randomized patients who received at least one dose of the study drug. Analysis of the Safety population will be done according to the treatment received (as treated).

In addition:
- Nonrandomized but treated patients will not be part of the safety population; however, their safety data will be presented separately
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized
- For patients receiving more than 1 IMP during the trial, the treatment group allocation for as-treated analysis will be the treatment group for which the patient received the first dose.

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In such cases, individual patient listings will be provided for each treatment group with treatment start and end date for each treatment exposed.

### 2.3.3  PK population

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing serum concentration available for PK analysis following the first dose of study drug.

### 2.3.4  ADA population

The ADA population includes all patients who had at least 1 post-baseline valid ADA sample following the first dose of study drug.

## 2.4  STATISTICAL METHODS

### 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 each treatment group.  Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Parameters will be summarized based on the mITT populations.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

Medical and surgical history will be summarized by SOC and PT sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC in total group (including all the randomized patients). P-values on 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  Concomitant medications

Concomitant medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the generic names.  All ATC codes corresponding to a medication will be summarized. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication; therefore, patients may be counted several times for the same medication.

Investigational medications are not coded, a category 'Investigational medications' will be used for these medications if applicable. The tables for concomitant medications will be sorted by

decreasing frequency of anatomic category followed by all other generic names based on the incidence of the total group (including all the randomized patients). In case of equal frequency regarding anatomic categories (respectively, generic names), alphabetical order will be used.

A listing of rescue medications will be provided including the following information:
- Start and end dates
- WHODD Preferred term
- Dose, unit and route
- ATC level 2 and ATC level 4

### 2.4.3  Extent of investigational medicinal product exposure and compliance

#### 2.4.3.1  Extent of investigational medicinal product exposure

Patients will receive a single dose of study drug on Day 1.  Patients may receive a second dose with study drug (based on the original treatment group assigned) 24 to 48 hours after the first dose, if they meet prespecified criteria.

Duration of IMP exposure will be analyzed by summarizing the number of doses patient received by treatment group in the safety population.

A listing will be provided for all study drug administered including the following information:
- Infusion rate (units: mL/h)
- Side and location of drug administration
- Start and end time
- Duration of intravenous infusion
- total dose injected (yes/no)
  - If no and not related to any AE, reason for not administration of total planned dose (Device problem, patient decision, other)
- Evidence of infusion reaction
- infusion interruptions
  - If yes, whether re-administered (yes/no)

#### 2.4.3.2  Compliance

The percentage of compliance, defined as the number of patients who fully completed infusion of the first study drug divided by number who received study drug, will be presented by treatment group based on the safety population.

## 2.4.4　Analyses of efficacy endpoints

Table 3 below summarizes the analyses for each type of efficacy endpoints in general.

**Table 3 – Summary of analyses for each type of efficacy endpoint**

| Type of endpoint | Statistical method | Graphical presentation |
|---|---|---|
| Time-to-event | Log-rank test (stratified) Cox-PH model (stratified) | KM curve |
| % of patients over time | CMH test (stratified) Descriptive statistics | Bar plot over time |
| % of patients at end | CMH test (stratified) Descriptive statistics | Bar plot |
| Continuous variable over time | ANCOVA model Descriptive statistics | Line plot over time |
| Continuous variable at end | ANCOVA model Descriptive statistics | Histogram |

For time to event analysis, the time to event duration is calculated as:

Date of first occurrence/episode of the event – date of first dose + 1.

### 2.4.4.1　Analysis of primary efficacy endpoint(s)

The primary efficacy analysis will be pairwise comparisons between sarilumab doses (400 mg and 200 mg) and placebo with respect to the primary endpoint, time to improvement of 2 points in clinical status assessment from baseline using the 7-point ordinal scale, using a log-rank test stratified by randomization stratum with treatment as a fixed factor in the mITT population. P-values for the pairwise comparison of each sarilumab dose versus placebo will be provided.

Hazard ratios for the estimation of treatment effect of each sarilumab dose compared to placebo will be provided using Cox proportional hazards model stratified by the randomization stratum with treatment as a covariate, along with 2-sided confidence intervals. Kaplan-Meier (KM) plot and the median time-to-improvement of 2 points will also be provided by treatment groups.

Superiority of sarilumab over placebo will be declared if the null hypothesis is rejected at the 5% (2-sided) significance level following the multiplicity control procedure specified in Section 2.4.4.3.

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Patients who have an improvement of 2-points in clinical assessment or discharge (other than death) will be considered as events, while patients who do not experience improvement of 2-points will be censored at the last observation time point. Patients who take rescue medication in the study without improvement of 2-points before that will be censored at the date of rescue medication started.

In addition, the proportion of patients with at least 2-point improvement from baseline at each day post-baseline will be provided using descriptive statistics. Graphical presentations (bar charts) will be used to examine trends over time.

The analyses using the log-rank test and Cox PH model specified above will be repeated for the severe patients and critical patients at baseline as recorded on CRFs.

**Baseline clinical status** is defined as the worse (lower) value of screening visit and Day 1 prior to dosing. If there is a tie, flag Day 1 as baseline. Baseline values are 2, 3, 4, 5, or 6. Values 1 and 7 do not apply (if 1 or 7 appear, then data query is needed.)

**Post-baseline clinical status** values range from 1 through 7 on ordinal scale and data will be as recorded on the ordinal scale eCRF.

Handling of death or discharge on clinical status assessment (post-baseline)

For patients who die, the clinical status recorded on the day of death will be replaced with "1=Death" and this value will be carried forward for all subsequent study days until end of study (Day 60). Death date may be obtained from Adverse Events or Disposition CRFs or phone call at Day 60 (end of study).

For patients who discharge early (other than death), the clinical status recorded on the earliest hospital discharge date will be replaced with 7 (not hospitalized), and this value will be carried forward for all subsequent study days until end of study (Day 60). Hospital discharge information (discharge date and discharge reason) may be obtained from the Discharge Reason eCRF. If there is subsequent hospitalization, the clinical status will not be replaced by 7 after the second hospitalization.

Handling of missing data on clinical status assessment (post-baseline)

For patients who are alive and not discharged (ie, still hospitalized), missing clinical status value (ordinal scale) on a given study day will be imputed using data on the type of oxygen delivery device used by the patient on that day (last type of device used if multiple types were used in a day).

Clinical status = 2 (if using invasive mechanical ventilation or ECMO), or

= 3 (if using non-invasive mechanical ventilation or high-flow nasal cannula), or

= 4 (if using nasal cannula, simple face mask, or non-rebreather face mask) or

= 5 (if not using supplemental oxygen)

**Sensitivity analysis**

The PPS and ITT will be used for sensitivity analysis of the primary efficacy endpoint, as described above.

**Subgroup analyses**

Descriptive analyses will be performed on the primary endpoint to summarize the treatment effect of each sarilumab dose versus placebo by the following variables:

- Age (<median, >=median)
- Age group ($\geq$18 and <64, $\geq$65 and <84, $\geq$85 years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, Other). Note: Japanese will be grouped with Asian, a group with less than 5 patients in any treatment may be grouped with 'Other'
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Severity of illness (per IRT) (Severe, Critical)
- Severity of illness (as recorded on CRFs) (Severe, Critical)
- Systemic corticosteroids use (per IRT) (Yes, No)
- Systemic corticosteroids use (as recorded on CRFs) (Yes, No)
- Fever status at baseline (Yes, No)
- Pneumonia present based on historical chest X-Ray, CT scan or MRI or lung auscultation (Yes, No)
- Any symptom of Fever, Cough, or Dyspnea (Yes, No)
- Time from dyspnea onset to baseline (<=5 days, >5 days). Note: patients with no dyspnea will be classified as <=5 days
- SpO2/FiO2 ratio (<median, >=median)
- CRP level (<median, >=median)
- Duration of hospitalization prior to first dose (<7 days, >=7 days);
- Number of study drug administration (1, 2)

Additional subgroups may be added as needed. The treatment effects will be estimated using hazard ratio (sarilumab compared to placebo) in the subgroups using the same analysis model as for the primary efficacy endpoint as described previously (without stratification factor for the stratification-related subgroups). In addition, p-value for the interaction of treatment by subgroup effect will be provided. Graphical presentation of the results (ie, forest plot) for each sarilumab dose versus placebo will also be provided.

### 2.4.4.2 Analyses of secondary efficacy endpoints

**Key secondary endpoint**

The percentage of patients alive at Day 29 will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by randomization strata of severity of illness and corticosteroid use in the mITT population. The difference in proportions of patients for each Sarilumab dose compared to placebo (sarilumab - placebo), along with associated 2-sided 95% confidence levels, and p-value will be provided.

Superiority of sarilumab over placebo will be declared if the null hypothesis is rejected at the 5% (2-sided) significance level following the multiplicity control procedure specified in Section 2.4.4.3.

In addition, bar plot for the proportion of patients alive at Day 29, KM curves for the overall survival will be provided by treatment group. Hazard ratios for the estimation of treatment effect of each sarilumab dose compared to placebo will be provided using Cox proportional hazards model stratified by the randomization stratum with treatment as a covariate, along with 2-sided confidence intervals.

These analyses will be repeated for the severe patients and critical patients at baseline as recorded on CRFs.

**Other secondary endpoints**

Details for analyses and derivation of the variables associated with the other secondary endpoints specified in Section 2.1.3.2 are detailed below.

<u>7-point ordinal scale</u>

The percent of patients with each category of the 7-point ordinal scale observed value at each day will be summarized using descriptive statistics. Graphical presentations (stacked bar charts) will also be used to examine trends over time.

*Analysis of endpoint #1: proportion of patients with one-point improvement from baseline*

Proportion of patients with at least 1-point improvement from baseline at Day 4, 7, 15, 21, and 29 will be analyzed using the same analysis model as for the key secondary endpoint as described previously. Graphical presentations (bar charts) will be used to examine trends over time.

*Analysis of endpoint #2: Mean change in 7-point ordinal scale from baseline*

Changes from baseline in the 7-point ordinal scale for Day 4, 7, 15,21, 29 (or until discharge) will be analyzed using an ANCOVA model with treatment group and randomization strata as fixed effects and baseline value as a covariate. The least squares (LS) treatment mean difference from placebo with standard error, along with corresponding 95 % confidence interval and p-value will be provided. Graphical presentations (line plot with mean and error bar) will also be used to examine trends over time using mean values ($\pm$SE) and mean changes from baseline ($\pm$SE).

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The 7-point ordinal scale at each day and their changes from baseline will also be summarized for each treatment group through descriptive statistics including mean, median, standard deviation, minimum and maximum.

<u>Fever</u>

Body temperature is collected using varying methods (the routes in eCRF are axillary, auricular, oral, rectal) at multiple timepoints each day.

**Baseline body temperature** is defined as the highest temperature at any time prior to first dose.

**Post-baseline body temperature** is defined as the highest temperature from each day among all temperatures from different timepoints (morning, evening, etc).

Patients body temperature and its change from baseline will be summarized at each day by treatment group by timepoint over the study period. Graphical presentations (line plot with mean and error bar) will also be used to examine trends over time using mean values (±SE) and mean changes from baseline (±SE).

All temperatures will be converted to oral values as following:

- Rectal/Auricular subtract 0.6 deg C = Oral deg C
- Axillary add 0.6 deg C = Oral deg C

*Analysis of endpoint #3: time to resolution of fever*

Resolution of fever is defined as body temperature (≤36.6°C [axilla], or ≤37.2 °C [oral], or ≤37.8°C [rectal or auricular]) for at least 2 consecutive days without antipyretics or until discharge, whichever is sooner.

The analysis will be performed similarly to the primary endpoint.

Patients who achieved resolution of fever or discharge (other than death) will be considered as events, while patients who do not experience resolution of fever will be censored at the end of study. Patients who started rescue therapy or died in the study will not be considered as having an endpoint event and will be censored at the earlier date of death or rescue therapy start date. Patients who do not have fever at baseline will be censored at the first dose date.

*Analysis of endpoint #5: the number of days with fever*

Fever is defined as body temperature >37.4°C (axillary), or >38°C(oral), or >38.4°C (rectal or auricular).

The number of days with fever will be analyzed using the ANCOVA model with treatment group and randomization strata as fixed effects for patients alive by Day 29. The LS treatment mean difference from placebo with standard error, along with corresponding 95 % confidence interval and p-value will be provided.

Summary statistics with mean, median, standard deviation, minimum and maximum will be provided. Histogram will be provided to illustrate the distribution of days with fever.

In addition, the percent of days with fever (100*number of days with fever divided by number of days of follow-up, defined as the earlier date of death or discharge or last visit up to Day 29) for all patients, will be analyzed using the ANCOVA model with treatment group and randomization strata as fixed effects.

Improvement in Oxygenation

Improvement in oxygenation is defined as increasing in SpO2/FiO2 of 50 or greater compared to the nadir SpO2/FiO2. Nadir SpO2/FiO2 is the nadir (lowest value) at any point in the study, and looking forward, an improvement in oxygenation is increase of 50 or greater from nadir value for at least 48 hours. If nadir is observed on 2 or more different days post baseline, the day of the first occurrence of nadir will be used.

**Baseline SpO2/FiO2 ratio** is defined as the last available ratio prior to first dose.

**Post-Baseline SpO2/FiO2** ratio is defined as the worst (minimum) value in each day.

For derivation of FiO2, please see conversion table in Section 2.5.2.

***Analyses of endpoint #4: time to resolution of fever and improvement in oxygenation,***
***#9: time to improvement in oxygenation, and***
***#14: time to saturation >=94% on room air***

The analysis of these endpoints will be performed similarly to the primary endpoint.

Patients who do not experience the event under analysis will be censored at the last observation time point. Patients who die or take rescue medication in the study without experiencing the event will be censored at the earlier date of death or rescue medication started.

***Analyses of endpoint #11: days of hypoxemia,***
***#12: days with supplemental oxygen use,***
***#13: days of resting respiratory rate >24 breaths/min, and***
***#15: ventilator free days in the first 28 days***

The analysis of these endpoints will be performed using the ANCOVA model with treatment group and randomization strata as fixed effects for patients alive by Day 29. The LS treatment mean difference from placebo with standard error, along with corresponding 95 % confidence interval and p-value will be provided. Patient discharged early will be considered as ventilator free until the next hospitalization (if applicable).

Summary statistics with mean, median, standard deviation, minimum and maximum will be provided. Histogram will be provided to illustrate the distribution.

In addition, the percent of days with each endpoint (100*number of days with the endpoint divided by number of days of follow up, defined as the earlier date of death or discharge or last

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visit up to Day 29) for all patients, will be analyzed using the ANCOVA model with treatment group and randomization strata as fixed effects.

***Analyses of endpoint #10: % of patients alive off oxygenation at Day 29, and***
***#16: % of patients with initiation of mechanical ventilation, non-invasive ventilation, or use of high flow nasal cannula, and***

These endpoints will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by randomization strata. The difference in proportions of patients for each Sarilumab dose compared to placebo (sarilumab - placebo), along with associated 2-sided 95% confidence levels, and p-value will be provided.

Bar plots will also be provided to illustrate the difference among treatments.

NEWS2

Please find NEWS2 score calculation and details in Section 2.5.2.

***Analyses of endpoint #6: Time to change in National Early Waring Score 2 (NEWS2) from baseline, and***
***#7: Time to NEWS2 of <2 and maintained for 24 hours***

The analysis for time to change in NEWS2 from baseline will be performed by evaluating the proportion of patients with clinical risk over time in each category (Low: 0-4; Low-medium: 3 in any individual parameter; Medium: 5-6; High: ≥7). The pattern of patients in the categories shifting from baseline and over time will be examined with no formal testing.

The time to NEWS2 < 2 and maintained for 24 hours endpoint will be analyzed similarly to the primary endpoint.

Patients who do not experience endpoint event under analysis will be censored at the last observation time point. Patients who die or take rescue medication in the study without experiencing the event will be censored at the earlier date of death or rescue medication started.

***Analyses of endpoint #8: Mean change from baseline to Day 4, 7, 15, 21, 29 in NEWS2***

Change from baseline in NEWS2 score at Day 4, 7, 15, 21, and 29 will be analyzed using an ANCOVA model with treatment group and randomization strata as fixed effects, and baseline value as a covariate. The least squares (LS) treatment mean difference from placebo with standard error, along with corresponding 95 % confidence interval and p-value will be provided. Graphical presentations (line plot with mean and error bar) will also be used to examine trends over time using mean values (±SE) and mean changes from baseline (±SE).

NEWS2 score at each day and their changes from baseline will be summarized for each treatment group through descriptive statistics including mean, median, standard deviation, minimum and maximum.

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ICU use, rescue medication, hospitalization and other

### Analyses of endpoint #17: % of patients requiring rescue medication during the 28-day period, #18: % of patients with ICU use (among those not in an ICU at baseline)

These endpoints will be analyzed using a CMH method stratified by randomization strata. The difference in proportions of patients for each Sarilumab dose compared to placebo (sarilumab - placebo), along with associated 2-sided 95% confidence levels, and p-value will be provided.

Bar plots will be provided to illustrate the difference among treatments. Summary of immunosuppressive medications used as rescue therapy over time will also be provided.

### Analyses of endpoint #19: Days of hospitalization among survivors

Analysis of days of hospitalization among survivors will be performed using the ANCOVA model with treatment group and randomization strata as fixed effects. The LS treatment mean difference from placebo with standard error, along with corresponding 95 % confidence interval and p-value will be provided.

Summary statistics with mean, median, standard deviation, minimum and maximum will be provided. Histogram will be provided to illustrate the distribution.

In addition, the percent of patients died or "on a ventilator", off oxygenation, and discharged will be summarized by treatment overtime, respectively. The time from first dose to discharge will also be summarized.

### 2.4.4.3 Multiplicity issues

Multiplicity will be controlled for the primary analysis (ie, Day 29). Final analysis (ie, Day 60) will be supportive.

For the primary and key secondary endpoints, multiplicity will be controlled via a hierarchical testing procedure in the following order:

1. Primary endpoint sarilumab 400 mg versus placebo
2. Key secondary endpoint sarilumab 400 mg versus placebo
3. Primary endpoint sarilumab 200 mg versus placebo
4. Key secondary endpoint sarilumab 200 mg versus placebo

If one sarilumab dose is discontinued for safety reasons, then all comparisons versus placebo for that dose will be removed and the remaining comparisons will be tested in the order specified above.

### 2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group.

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*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 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, vital signs, and ECG (see Appendix A)

- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event 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 treatment-emergent adverse event period by treatment group on the safety population.

- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. Summaries will include the endpoint value. The endpoint value is commonly defined as the value collected at the same day/time of the last dose of investigational product. If this value is missing, this endpoint value will be the closest one prior to the last dose intake.

- Selected safety analyses will be summarized by age group, gender, racial subgroups, and any pertinent subgroups as appropriate (eg, number of doses administered).

### 2.4.5.1 Analyses of adverse events

*Generalities*

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pretreatment and posttreatment adverse events will be described separately.

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

Adverse event incidence tables will be sorted by SOC internationally agreed order and HLGT, HLT, PT by alphabetic order. For adverse event incidence tables presented by SOC and PT, they will be sorted by the internationally agreed SOC order and by decreasing incidence of PTs based

on the Sarilumab 400 mg IV group within each SOC, for the number (n) and percentage (%) of patients experiencing an adverse event. 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 treatment group.

*Analysis of all treatment-emergent adverse events*

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing total number or number (%) of patients with any
  - Treatment-emergent adverse event
  - Serious treatment-emergent adverse event
  - Severe treatment-emergent adverse event
  - AESI
  - Treatment-emergent adverse event leading to death
  - TEAE leading to study drug interruption or discontinuation
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event.
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event.
- All treatment-emergent adverse events by primary SOC, PT and CTC grade, showing the number (%) of patients with at least 1 treatment-emergent adverse event.
- All treatment-emergent adverse events regardless of relationship and related by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event.
- All treatment-emergent adverse events leading to study drug interruption or discontinuation by Primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event.

*Analysis of all treatment emergent serious adverse event(s)*

- All treatment-emergent serious adverse events by primary SOC and PT showing the number (%) of patients with at least 1 serious treatment-emergent adverse event.
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event.

*Analysis adverse event of special interest*

Unless otherwise specified, AESI will be summarized during the TEAE period by prespecified-grouping (AE category of interest), showing the number (%) of participants, sorted by decreasing

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frequency of PT. In addition, summary of TEAE of infusion reactions, ALT increase, and infection events will be provided.

Listings of all adverse events, serious adverse events and AESIs during the study will be provided.

### 2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died during the study

- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC and PT.

Listing will be provided for all deaths with flags indicating TEAE period or post-treatment period status.

### 2.4.5.3 Analyses of laboratory variables

Hematology, blood chemistry and urinalysis are performed in local laboratories in this study.

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 treatment group.  This section will be organized by biological function as specified in Section 2.1.4.3.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing

- Abnormal according to PCSA criterion or criteria

The incidence of abnormal laboratory values at any time during the TEAE period will be summarized in shift tables by biological function and treatment group 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

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

For bacterial infection testing, results will be summarized as number of patients (counts and percent) with negative and positive levels by treatment group.

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### 2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital sign variables (vital signs values and changes from baseline) will be calculated for each visit or study assessment (daily from baseline to Day 29) by treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of 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 for patients with at least one post-baseline PCSA values.

### 2.4.5.5 Analyses of physical examination

Physical examination data which is only collected at screening will not be summarized.

### 2.4.5.6 Analyses of electrocardiogram variables

Listing of patient ECG variables at screening will be provided.

### 2.4.5.7 Analyses of anti-sarilumab antibodies

The following summary will be provided separately for ADA positive patient, ADA negative patient.

#### 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
  - 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 TEAE period:

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

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

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

Plot of percentage of patients with treatment-emergent ADA positive response at each visit will be provided by treatment group.

Listing for ADA status will also be provided.

### *ADA and PK*

Descriptive summary of sarilumab concentrations in serum will be provided by ADA patient classifications (positive or negative) over time for the sarilumab treatment group by number of sarilumab doses.

### *ADA and clinical efficacy*

The primary and key secondary efficacy endpoints will be analyzed by ADA patient classifications (positive or negative).

### *ADA and clinical safety*

The safety assessment will focus on the following events:

- Hypersensitivity (standardized MedDRA query (SMQ): Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])
- IV infusion reaction (HLT: IV infusion reaction)
- TEAEs leading to permanent treatment discontinuations

Number (%) of patients with these events will be summarized by ADA patient classifications (positive or negative) for the sarilumab treatment group.

## 2.4.6  Analysis of pharmacokinetics

**Analysis of drug concentration data:**

The concentrations of sarilumab over time and pharmacokinetic parameters, as appropriate, will be summarized using descriptive statistics by treatment group and number of sarilumab doses using the PK population.

No formal statistical hypothesis testing will be performed.

### 2.4.7 Analysis of Pharmacodynamic and Exploratory Biomarker Data:

The concentrations of CRP, IL-6, and sIL-6R over time will be summarized using descriptive statistics by treatment group using the safety population. The analysis will include:

- Observed value, change from baseline and percent change from baseline by each sampling point through Day 29 /EoS.

- The figures of mean ± standard error (SE) versus scheduled sampling time points.

In addition, ANC will be analyzed similarly.

As an exploratory analysis, the percentage of patients with SARS-CoV-2 positive (either nasopharyngeal swab or PCR) over time will be summarized using the safety population.

The relationship between d-dimer, ferritin, LDH, IL-6, neutrophil:lymphocyte ratio and the clinical assessment using the 7-point ordinal scale will be explored.

## 2.5 DATA HANDLING CONVENTIONS

### 2.5.1 General conventions

The following formulas will be used for computations of parameters.

*Demographic formulas:*

Age at baseline is calculated as follows:

$$Age = (informed\ consent\ date - birth\ date)/365.25$$

BMI is calculated as follows:

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

### 2.5.2 Data handling conventions for secondary efficacy variables

**SpO2**

If SpO2 is missing, then that value will be imputed using last observation carried forward.

**FiO2**

FiO2 will be derived as following.

- For high flow nasal cannula, non-invasive ventilation, invasive ventilation, use FiO2 as reported on eCRF.

- For Nasal cannula, simple face mask, non-rebreather face mask, FiO2 will be converted based on below table.

| Method | Oxygen flow rate O₂ flow (l/min) | Fraction of Inspired Oxygen [FiO₂] (%) |
|---|---|---|
| Nasal cannula | 1 | 24 |
| | 2 | 28 |
| | 3 | 32 |
| | 4 | 36 |
| | 5 | 40 |
| | 6 | 44 |
| | >=7 | (O2*4) + 20.  Maximum will be 100 |
| Simple face mask | 5 | 40 |
| | 6 | 50 |
| | 7 | 55 |
| | 8 | 60 |
| | 9 | 65 |
| | >=10 | 70 |
| Non-rebreather face mask | <6 | 60 |
| | 6 | 60 |
| | 7 | 70 |
| | 8 | 80 |
| | 9 | 90 |
| | 10 | 95 |
| | >=10 | 95 |

Note: If FiO2 data is entered in the CRF for above devices, ignore value and derive as above. Some values for FiO2 (not in the source table) are imputed according to a trend.

- If 'Other' oxygen device, use FiO2 value if reported on eCRF. Otherwise, keep missing.

- If patient receives ECMO, alone or in combination with any other oxygen supplementation, use FiO2 for ECMO only reported on eCRF.

- If patient is not on supplemental oxygen, impute with FiO2=21%.

**NEWS2**

NEWS2 consists of 6 physiological parameters collected in various eCRF forms:
- Consciousness
- Respiratory rate
- Oxygen saturation (SpO2)
- Pulse rate
- Systolic blood pressure
- Temperature

In addition, information on whether patients require supplemental oxygen and whether patient experienced chronic hypercapnic respiratory failure (collected in Pneumonia Status at Screening form) are required in the calculation of the NEWS2 score.

Calculation of NEWS2 score

NEWS2 score is calculated according to below chart.
- For patients with a history of or current chronic hypercapnic respiratory failure, use the dedicated section (SpO2 Scale 2) in the chart.
- For patients who received oxygen supplementation, the score is uplifted by 2 points.

| Physiological parameter | Score | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3 | 2 | 1 | 0 | 1 | 2 | 3 |
| Respiration rate (per minute) | ≤8 | | 9–11 | 12–20 | | 21–24 | ≥25 |
| SpO₂ Scale 1 (%) | ≤91 | 92–93 | 94–95 | ≥96 | | | |
| SpO₂ Scale 2 (%) | ≤83 | 84–85 | 86–87 | 88–92 ≥93 on air | 93–94 on oxygen | 95–96 on oxygen | ≥97 on oxygen |
| Air or oxygen? | | Oxygen | | Air | | | |
| Systolic blood pressure (mmHg) | ≤90 | 91–100 | 101–110 | 111–219 | | | ≥220 |
| Pulse (per minute) | ≤40 | | 41–50 | 51–90 | 91–110 | 111–130 | ≥131 |
| Consciousness | | | | Alert | | | CVPU |
| Temperature (˚C) | ≤35.0 | | 35.1–36.0 | 36.1–38.0 | 38.1–39.0 | ≥39.1 | |

NEWS2 thresholds and triggers

| NEW score | Clinical risk | Response |
|---|---|---|
| Aggregate score 0–4 | Low | Ward-based response |
| Red score Score of 3 in any individual parameter | Low–medium | Urgent ward-based response* |
| Aggregate score 5–6 | Medium | Key threshold for urgent response* |
| Aggregate score 7 or more | High | Urgent or emergency response** |

* Response by a clinician or team with competence in the assessment and treatment of acutely ill patients and in recognising when the escalation of care to a critical care team is appropriate.

**The response team must also include staff with critical care skills, including airway management.

Imputation for NEWS2 component

If any component (physiological parameter) is missing, then that value will be imputed using last observation carried forward.

### 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 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 and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and posttreatment medication.

*Handling of adverse events with missing or partial date/time of onset*

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

*Handling of adverse events when date and time of first investigational medicinal product administration is missing*

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

*Handling of missing assessment of relationship of adverse events to investigational medicinal product*

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

*Handling of missing severity of adverse events*

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 summary table.

*Handling of potentially clinically significant abnormalities*

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

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For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this 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 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

*Handling of missing discharge date*

If a patient was discharged but the discharge date was missing, impute with last visit date.

### 2.5.4  Windows for time points

Visit windows based on days relative to the first IMP dose will be used to map the lab measurements to each scheduled visit (see Appendix B). The following rule will be applied when mapping the measurements to the visit:

1. For the same laboratory parameter, 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 (in case of tie select the latest). If there is no scheduled measurement within the visit window, the unscheduled measurement that is closest to the target date will be used (in case of tie select the latest).

2. 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.

### 2.5.5  Unscheduled visits

Unscheduled visit measurements of laboratory data and vital signs will be used in PCSA analysis, computation of baseline, and will also be assigned to the appropriate visit window for the by-visit summaries.

### 2.5.6  Pooling of centers for statistical analyses

Not applicable.

# 3    INTERIM ANALYSIS

An interim analysis is planned to be performed when approximately 50% of total planned number of patients (~200) are randomized. The efficacy endpoints will be analyzed using the same methods described in the efficacy analyses section (Section 2.1.3). The key secondary endpoint will be modified to be the percent of patients alive at Day 15.

The purpose of the interim analyses is to obtain an understanding of the possible drug effect in the population under study.  An administrative alpha of 0.001 will be spent at interim analysis. Due to the conservative amount of alpha spent at interim, no alpha adjustment will be made for the primary analysis when the last patient randomized of the whole study reaches Day 29 (or planned Day 29 if the patient is discharged or leaves the study early), or the supportive final analysis at Day 60.

The interim analyses will be performed by an external statistical analysis center which is separate from personnel involved in the trial conduct. The unblinded results can only be viewed by a small group of senior sponsor individuals, who are separate from sponsor personnel involved in the conduct of the study. People involved in the conduct of the study (Patients, Investigators, Study Team, and Project Team) will have no access to the interim analysis results. Sponsor may decide to make changes to the dose and/or alter disease category based on the interim results.

The interim analysis is planned to mainly include the following:

- Demographics and baseline characteristics
- 7-point ordinal scale (observed value and change from baseline category, time to improvement of at least two points, proportion of patients with at least 2-point improvement)
- Patient survival status
- Overview of TEAE
- Number of patients with SAE

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# 4    DATABASE LOCK

The primary analysis is planned when the last patient randomized reaches Day 29 (or planned Day 29 if the patient is discharged or leaves the study early). Final analysis will be performed at study end (ie, Day 60).

# 5    SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.2 or higher.

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# 6 REFERENCES

Not applicable.

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# 7    LIST OF APPENDICES

Appendix A:    Potentially clinically significant abnormalities (PCSA) criteria

Appendix B:    Visit Windows based on day ranges

Appendix C:    AESI and search criteria

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## Appendix A    Potentially clinically significant abnormalities criteria

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**

**for phase 2/3 studies (oncology excepted)**

*(From BTD-009536 " Analysis and reporting of safety data from clinical trials through the Clinical Study Report"– Version 3 – 21-MAY-2014)*

| Parameter | PCSA | Comments |
|---|---|---|
| **Clinical Chemistry** | | |
| ALT | By distribution analysis:<br>>3 ULN<br>>5 ULN<br>>10 ULN<br>>20 ULN<br>**Additional analysis*:**<br>>1 – 1.5 ULN<br>>1.5 – 3 ULN<br>>3 - 5 ULN<br>>5 – 8 ULN<br>> 8 ULN | Enzymes activities must be expressed in ULN, not in IU/L.<br>Concept paper on DILI – FDA draft Guidance Oct 2007.<br>Internal DILI WG Oct 2008.<br>Categories are cumulative.<br>First row is mandatory. Rows following one mentioning zero can be deleted. |
| AST | By distribution analysis:<br>>3 ULN<br>>5 ULN<br>>10 ULN<br>>20 ULN<br>**Additional analysis*:**<br>>1 – 1.5 ULN<br>>1.5 – 3 ULN<br>>3 - 5 ULN<br>>5 – 8 ULN<br>> 8 ULN | Enzymes activities must be expressed in ULN, not in IU/L.<br>Concept paper on DILI – FDA draft Guidance Oct 2007.<br>Internal DILI WG Oct 2008.<br>Categories are cumulative<br>First row is mandatory. Rows following one mentioning zero can be deleted. |
| Alkaline Phosphatase | >1.5 ULN | Enzymes activities must be expressed in ULN, not in IU/L.<br>Concept paper on DILI – FDA draft Guidance Oct 2007.<br>Internal DILI WG Oct 2008. |

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**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**

**for phase 2/3 studies (oncology excepted)**

*(From BTD-009536 " Analysis and reporting of safety data from clinical trials through the Clinical Study Report"– Version 3 – 21-MAY-2014)*

| Parameter | PCSA | Comments |
|---|---|---|
| Total Bilirubin | >1.5 ULN<br>>2 ULN | Must be expressed in ULN, not in µmol/L or mg/L.<br>Concept paper on DILI – FDA draft Guidance Oct 2007.<br>Internal DILI WG Oct 2008.<br>Categories are cumulative.<br>First row is mandatory. Rows following one mentioning zero can be deleted. |
| Conjugated Bilirubin | >35% Total Bilirubin and TBILI>1.5 ULN<br><br>**Additional analysis*:**<br>>1.5 ULN<br>>2 ULN | Conjugated bilirubin dosed on a case-by-case basis.<br>PCSA to be retrieved manually |
| Unconjugated bilirubin | **Additional analysis*:**<br>>1.5 ULN<br>>2 ULN | Must be expressed in ULN, not in µmol/L or mg/L.<br>Categories are cumulative. |
| ALT and Total Bilirubin | ALT>3 ULN and TBILI>2 ULN | Concept paper on DILI – FDA draft Guidance Oct 2007.<br>Internal DILI WG Oct 2008.<br>To be counted within a same treatment phase, whatever the interval between measurement. |
| CPK** | >3 ULN<br>>10 ULN | FDA Feb 2005.<br>Am J Cardiol April 2006.<br>Categories are cumulative.<br>First row is mandatory. Rows following one mentioning zero can be deleted. |
| Creatinine | ≥150 µmol/L (Adults)<br>≥30% change from baseline<br>≥100% change from baseline | Benichou C., 1994. |

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**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**

**for phase 2/3 studies (oncology excepted)**

*(From BTD-009536 " Analysis and reporting of safety data from clinical trials through the Clinical Study Report"– Version 3 – 21-MAY-2014)*

| Parameter | PCSA | Comments |
|---|---|---|
| CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation) | <15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR) | FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling |
| eGFR** (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation) | <15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR) | FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling |
| Uric Acid Hyperuricemia Hypouricemia | >408 µmol/L <120 µmol/L | Harrison- Principles of internal Medicine 17th Ed., 2008. |
| Blood Urea Nitrogen | ≥17 mmol/L | |
| Chloride | <80 mmol/L >115 mmol/L | |
| Sodium | ≤129 mmol/L ≥160 mmol/L | |
| Potassium | <3 mmol/L ≥5.5 mmol/L | FDA Feb 2005. |
| Total Cholesterol | ≥7.74 mmol/L **≥6.2 mmol/L\*** | Threshold for therapeutic intervention. |
| LDL | **≥4.1 mmol/L\*** ≥4.9 mmol/L | |
| Triglycerides | ≥4.6 mmol/L **≥5.6 mmol/L\*** | Threshold for therapeutic intervention. |
| Lipasemia** | ≥3 ULN | |
| Amylasemia** | ≥3 ULN | |

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**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**

**for phase 2/3 studies (oncology excepted)**

*(From BTD-009536 " Analysis and reporting of safety data from clinical trials through the Clinical Study Report"– Version 3 – 21-MAY-2014)*

| Parameter | PCSA | Comments |
|---|---|---|
| Glucose | | |
| Hypoglycaemia | ≤3.9 mmol/L and <LLN | ADA May 2005. |
| Hyperglycaemia | ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) | ADA Jan 2008. |
| HbA1c | >8% | |
| Albumin | ≤25 g/L | |
| CRP | >2 ULN or >10 mg/L (if ULN not provided) | FDA Sept 2005. |
| **Hematology** | | |
| WBC | <3.0 Giga/L (Non-Black); <2.0 Giga/L (Black)<br>≥16.0 Giga/L | Increase in WBC: not relevant.<br>To be interpreted only if no differential count available. |
| Lymphocytes | **<0.5 Giga/L\***<br>**≥0.5 Giga/L - LLN\***<br>>4.0 Giga/L | |
| Neutrophils | <1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)<br>**<1.0 Giga/L\*** | International Consensus meeting on drug-induced blood cytopenias, 1991.<br>FDA criteria. |
| Monocytes | >0.7 Giga/L | |
| Basophils | >0.1 Giga/L | |
| Eosinophils | >0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L) | Harrison- Principles of internal Medicine 17th Ed., 2008. |
| Hemoglobin | ≤115 g/L (Male); ≤95 g/L (Female)<br>≥185 g/L (Male); ≥165 g/L (Female)<br><br>Decrease from Baseline ≥20 g/L | Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L). |
| Hematocrit | ≤0.37 v/v (Male) ; ≤0.32 v/v (Female)<br>≥0.55 v/v (Male) ; ≥0.5 v/v (Female) | |

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**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES**

**for phase 2/3 studies (oncology excepted)**

*(From BTD-009536 " Analysis and reporting of safety data from clinical trials through the Clinical Study Report"– Version 3 – 21-MAY-2014)*

| Parameter | PCSA | Comments |
|---|---|---|
| RBC | ≥6 Tera/L | Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria. |
| Platelets | **< 50 Giga/L\*** **≥ 50 - 100 Giga/L\*** ≥700 Giga/L | International Consensus meeting on drug-induced blood cytopenias, 1991. |
| **Urinalysis** | | |
| pH | ≤4.6 ≥8 | |
| **Vital signs** | | |
| HR | ≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm | To be applied for all positions (including missing) except STANDING. |
| SBP | ≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg | To be applied for all positions (including missing) except STANDING. |
| DBP | ≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg | To be applied for all positions (including missing) except STANDING. |
| Orthostatic Hypotension Orthostatic SDB Orthostatic DBP | ≤-20 mmHg ≤-10 mmHg | |
| Weight | ≥5% increase from baseline ≥5% decrease from baseline | FDA Feb 2007. |

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## Appendix B    Visit windows based on day ranges

**Table 4 – Time window for lab summaries**

| Visit Label | Target Day | Hematology, Chemistry | Bacterial infection testing |
|---|---|---|---|
| **Daily follow-up until hospital discharge or Day 29** | | | |
| Baseline | 1 | ≤1 | |
| Day 4 | 4 | 2-5 | |
| Day 7 | 7 | 6-10 | 2-10 |
| Day 15 | 15 | 11-17 | ≥11 |
| Day 21 | 21 | 18-24 | |
| Day 29 | 29 | ≥25 | |

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## Appendix C    AESIs and search criteria

**Table 5 – AESIs and search criteria**

| AESI flag | Search[a] criteria |
|---|---|
| Grade ≥2 infusion related reactions | Any Grade ≥2 (moderate) TEAE of infusion related reactions within 24 hours from the start of study drug infusion based upon CRF checkbox: Infusion Reaction and Yes to AESI event and Severity Grade ≥2. |
| Grade ≥2 hypersensitivity reactions | SMQ: Anaphylactic reaction, Hypersensitivity or Angioedema and Grade ≥2 (moderate) |
| Grade 4 neutropenia | ANC <500/mm$^3$ and CRF checkbox: Yes to AESI event |
| Grade 4 neutropenia with concurrent invasive infection[b] | ANC <500/mm$^3$ and Primary SOC: Infections and infestations within 1 week of ANC <500/mm$^3$ |
| Invasive bacterial or fungal infection[c] | Primary SOC: Infections and infestations |
| Alanine transaminase (ALT) increase | CRF checkbox: ALT Increase and Yes to AESI event |
| Overdose[d] | CRF checkbox:  Symptomatic overdose |

TEAE: Treatment-emergent adverse event

a   All SMQs are narrow search

b   Patients having both a Grade 4 Neutropenia and a concurrent infection event will be further reviewed by the medical team to confirm that the infection event is invasive.

c   Patients identified as having an infection event will be further reviewed by the medical team to confirm that the infection is invasive.

d   Standard AESI applies to all Sanofi studies

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