COV-AID Statistical Analysis Plan

TRIAL FULL TITLE	A prospective, randomized, factorial design, interventional study to compare the safety and efficacy of combinations of blockade of interleukin-6 pathway and interleukin-1 pathway to best standard of care in improving oxygenation and short- and long-term outcome of COVID-19 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome.
SAP VERSION	1.0
SAP VERSION DATE	5th March 2021
PROTOCOL VERSION	5.0
PROTOCOL VERSION DATE	3rd November 2020
EUDRACT NUMBER	2020-001500-41
CLINICALTRIALS.GOV IDENTIFIER	NCT04330638
TRIAL STATISTICIAN	Dr. Stefanie De Buyser (Biostatistics Unit, Faculty of Health Sciences and Medicine, Ghent University)
TRIAL CHIEF INVESTIGATOR	Prof. dr. Bart Lambrecht (Department of Internal Medicine & Pediatrics, Department of Respiratory Medicine, University Hospital Ghent)
SAP AUTHOR	Dr. Stefanie De Buyser (Biostatistics Unit, Faculty of Health Sciences and Medicine, Ghent University)
SAP REVIEWERS	Roos Colman (Biostatistics Unit, Faculty of Health Sciences and Medicine, Ghent University) Prof. dr. Marc Buyse (Interuniversity Institute for Biostatistics and statistical Bioinformatics, Data Science Institute, Hasselt University; International Drug Development Institute) Prof. dr. Catherine Legrand (Louvain School of Statistics, Biostatistics and Actuarial Sciences, Faculty of Science, Université catholique de Louvain)

Table of Contents

Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
AR	Adverse Reaction
ARDS	Acute Respiratory Distress Syndrome
CI	Confidence Interval
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DSMB	Data Safety Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
FEV1	Forced Expiratory Volume in 1 second
FiO_2	Fraction of inspired oxygen
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
HR	Hazard Ratio
ICU	Intensive Care Unit
IL	Interleukin
ITT	Intention To Treat
LDH	Lactate Dehydrogenase
PaO_2	Partial pressure of oxygen
RR	Risk Ratio
RV	Residual Volume
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. INTRODUCTION

1.1. Background and rationale

Coronavirus disease 2019 (COVID-19), a respiratory tract infection inflicted by a new coronavirus SARS-CoV-2, has evolved to a pandemic threat with unknown outcome.

Most people with COVID-19 develop mild respiratory illness with upper airway symptoms, taste and smelling loss, cough, malaise and transient fever (Stage I of disease). In approximately 15% of patients there is a second phase of the disease. Stage II occurs after approximately 7-10 days. It is accompanied by increasing respiratory symptoms, persistent fever, and shortness of breath, and requires hospitalization. A further 5% of patients develop stage III disease that requires admission to an intensive care unit (ICU) mostly due to acute respiratory distress syndrome (ARDS), sepsis and septic shock, multiorgan failure, including acute kidney injury and cardiac injury (Huang *et al*.). As patients progress from stage I to stage III, there are increasing signs of a systemic hyperinflammatory response, as reflected by increased levels of cytokines, CRP and ferritin.

A complex cytokine response that builds in infection is characterized by series of overlapping networks. Cytokines TNF and IL-1α and the chemotactic cytokines IL-8 and MCP-1 appear almost immediately after infection. This acute response is followed by a more sustained increase in IL-6. IL-6 is a key pro-inflammatory cytokine and an important mediator of fever and the acute phase response. Measurement of IL-6 concentration in peripheral blood has often been used to assess the intensity of systemic cytokine responses in patients with sepsis.

There are currently no treatments directed at halting the cytokine storm and acute lung injury to stop the progression from manageable hypoxia to frank respiratory failure and ARDS in patients with COVID-19 infection. Nevertheless, preventing cytokine release syndrome and avoiding progression from early hypoxic respiratory failure and mild acute lung injury to ARDS could have a huge impact on the foreseeable overflow of the ICU units.

We hypothesize that IL-6 and/or IL-1 are important mediators of the cytokine release syndrome and that blockade of IL-6 and/or IL-1 can halt the cytokine storm and acute lung injury. Therefore, the objective is to investigate if treatment to block IL-6 or IL-1 can reduce the time to clinical improvement compared to usual care in COVID-19 patients with hypoxia and signs of cytokine release syndrome. These two independent research questions will be examined in a multi-center non-blinded randomized controlled study with a 2x2 factorial design. Anakinra will be used as IL-1 blockade treatment. Siltuximab or tocilizumab will be used as IL-6 blockade treatment.

1.2. Study objectives

1.2.1. Primary objectives

The primary objectives of this study are to compare:

A. IL-1 blockade treatment versus no IL-1 blockade treatment
B. IL-6 blockade treatment versus no IL-6 blockade treatment

with respect to

- time to clinical improvement, with clinical improvement defined as either an increase of at least 2 points on the 6-category ordinal scale (from the status at randomization) or live discharge from the hospital,

in COVID-19 patients with hypoxia and signs of cytokine release syndrome.

1.2.2. Secondary objectives

1.2.2.1. Secondary objectives related to the primary endpoint

If the overall effect of IL-6 blockade treatment compared to no IL-6 blockade treatment on time to clinical improvement is statistically significant, then secondary objectives are to compare:

C. siltuximab treatment versus no IL-6 blockade treatment

D. tocilizumab treatment versus no IL-6 blockade treatment

with respect to

- time to clinical improvement.

If the individual effects of both siltuximab and tocilizumab compared to no IL-6 blockade treatment on time to clinical improvement are statistically significant, then a further secondary objective is to compare:

E. siltuximab versus tocilizumab

with respect to

- time to clinical improvement.

1.2.2.2. Secondary objectives related to secondary endpoints

Other secondary objectives of this study are to compare:

A. IL-1 blockade treatment versus no IL-1 blockade treatment

B. IL-6 blockade treatment versus no IL-6 blockade treatment

with respect to

- oxygenation (as measured by the ratio of partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2))
- all-cause mortality
- defervescence (the absence of fever for more than 48h without antipyretics)
- degree of illness (as measured by the Sequential Organ Failure Assessment (SOFA) score)
- laboratory values of ferritin levels.

If the overall effect of IL-6 blockade treatment compared to no IL-6 blockade treatment on a secondary endpoint is statistically significant, then further objectives are to compare:

C. siltuximab treatment versus no IL-6 blockade treatment

D. tocilizumab treatment versus no IL-6 blockade treatment

with respect to the respective secondary endpoint.

If the individual effects of both siltuximab and tocilizumab compared to no IL-6 blockade treatment are statistically significant on a secondary endpoint, then a further secondary objective is to compare:

E. siltuximab and tocilizumab

with respect to the respective secondary endpoint.

1.2.3. Exploratory objectives

1.2.3.1. Exploratory objectives related to the primary endpoint

- To test for an interaction between the effect of IL-1 blockade treatment and IL-6 blockade treatment on time to clinical improvement.
- To test if the effect of IL-1 blockade treatment on time to clinical improvement is modified by serum IL-1 level at the time of randomization.
- To test if the effect of IL-6 blockade treatment on time to clinical improvement is modified by serum IL-6 level at the time of randomization.
- To test if the effect of treatment on time to clinical improvement is modified by CRP (mg/L) at the time of randomization.
- To test if the effect of treatment on time to clinical improvement is modified by ventilation status at the time of randomization.

1.2.4. Safety objectives

To assess the overall safety of

- IL-1 blockade treatment with anakinra,
- IL-6 blockade treatment with siltuximab,
- IL-6 blockade treatment with tocilizumab,
- IL-1 blockade treatment with anakinra + IL-6 blockade treatment with siltuximab,
- IL-1 blockade treatment with anakinra + IL-6 blockade treatment with tocilizumab,

in terms of

- death
- microbiology (Nosocomial bacterial or invasive fungal infection)
- sepsis or septic shock
- adverse events and subclassifications thereof
- laboratory parameters at day 1, day 6, and day 15 or discharge (whichever comes first)
- vital signs at day 1, day 6, and day 15 or discharge (whichever comes first)

compared to usual care with no additional treatment in COVID-19 patients with hypoxia and signs of cytokine release syndrome.

1.3. Endpoints

1.3.1. Primary efficacy endpoint

The primary efficacy endpoint will be the time to clinical improvement, defined as the time from randomization to either an increase of at least two points on a 6-category ordinal scale (from the worst status at day of randomization) or live discharge from the hospital, whichever occurs first.

The 6-category ordinal scale:

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO;
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen
6. Not hospitalized

Patients who do not have experienced clinical improvement by the cut-off date for the primary analysis, will be censored at the date of their last registered day in hospital.

Patients who die before having experienced clinical improvement will be censored at the longest observed follow-up time for this event seen in the study.

1.3.2. Supportive endpoints related to the primary efficacy endpoint

To gain a better understanding of the already demonstrated effect on the primary endpoint, the following supportive endpoints will be examined:

- Time to clinical improvement (expressed in days), defined as the time from randomization to either an increase of at least two points on an 8-category ordinal scale (from the status at day of randomization) or live discharge from the hospital, whichever occurs first.

  This 8-category ordinal scale (based on the WHO R&D Blueprint, 2020) makes a further distinction between intubation + mechanical ventilation and ventilation + additional organ support – pressors, renal replacement therapy, Extracorporeal Membrane Oxygenation (ECMO):

  1. Death
  2. Hospitalized, ventilation + additional organ support – pressors, renal replacement therapy, ECMO
  3. Hospitalized, intubation and mechanical ventilation
  4. Hospitalized, non-invasive ventilation or high flow oxygen
  5. Hospitalized, oxygen by mask or nasal prongs
  6. Hospitalized, no oxygen therapy
  7. Ambulatory, limitation of activities
  8. Ambulatory, no limitation of activities

  All patients with hospital discharge (score 7 or 8) will be considered to have experienced the event (regardless of the relative improvement on the scale). The eCRF will not record the presence of limitation of activities in ambulatory patients, hence no distinction between score 7 or 8 can be made.

- Time since randomization until independence from supplemental oxygen or live discharge from the hospital, whichever occurs first.
- Absolute number of days without supplemental oxygen use up to 28 days after randomization
- Time since randomization until independence from mechanical ventilation
- Relative number of invasive ventilator days, relative to number of days alive the first 28 days after randomization
- Time since randomization until first use of high-flow oxygen devices, non-invasive or invasive mechanical ventilation, or death
- Absolute number of invasive ventilator-free days up to 28 days after randomization
- Time since randomization until live hospital discharge
- Absolute number of days in hospital
- Relative number of days in hospital, relative to number of days alive the first 28 days after randomization
- Absolute number of days in ICU
- Relative number of days in ICU, relative to number of days alive the first 28 days after randomization

1.3.3. Secondary efficacy endpoints and related supportive endpoints

To demonstrate additional effects and / or to provide evidence that a particular mechanism underlies a demonstrated clinical effect, the following secondary endpoints will be interpreted. If an effect can be demonstrated, related supportive endpoints will also be interpreted.

- Mean change from day 1 in PaO_2/FiO_2 at day 15 or discharge, whichever comes first.

  The PaO_2/FiO_2 ratio is measured in patients as a clinical indicator of hypoxemia. In some occasions it may be used as a trick for detecting an A-a gradient. The ratio is markedly dependent on FiO_2, with room air the FiO_2 is 21%.
- Mean ferritin level at day 6 (or discharge, whichever comes first)
- Mean SOFA score at day 6 (or discharge, whichever comes first)

  The SOFA score is a mortality prediction score calculated every 24 hours from admission until discharge using the worst parameters measured during the prior 24 hours. The score is based on the degree of dysfunction of six organ systems. It takes into account PaO_2, FiO_2, mechanical ventilation, platelet count, Glasgow Coma Scale, bilirubin concentration, mean arterial pressure or required administration of vasoactive agents, and creatinine concentration.

  Related supportive endpoints:
  - Mean slope of SOFA score over time
  - Mean SOFA score at day 15 (or discharge, whichever comes first)
- Time since randomization until death from all causes

  Related supportive endpoints:
  - All-cause mortality at day 28
  - All-cause mortality at week 10

  In addition to the registered data in the eCRF, mortality data will also be requested from the national registry after long-term follow-up.

- Time since randomization until absence of fever for more than 48h without antipyretics or live hospital discharge, whichever comes first

  Related supportive endpoint:

  - Absolute number of days with fever during hospital stay since randomization
- The first three secondary endpoints (mean change from day 1 in PaO_2/FiO_2 at day 15, mean ferritin level at day 6 , and mean SOFA score at day 6) will be considered as key secondary endpoints for which correction for multiple testing will be made.

1.3.4. Exploratory endpoints

- Mean CRP at day 6 (or discharge, whichever comes first)

1.3.5. Descriptive endpoints

- Score on the 6-category ordinal scale at day 15
- Score on the 6-category ordinal scale at 10-20 weeks
- Mean lung fibrosis score at 10-20 weeks
- Mean forced expiratory volume in 1 second (FEV1) at 10-20 weeks
- Mean forced vital capacity (FVC) at 10-20 weeks
- Mean functional residual capacity (FRC) at 10-20 weeks
- Mean residual volume (RV) at 10-20 weeks
- Mean diffusing capacity of the lungs for carbon monoxide (DLCO) at 10-20 weeks
- Mean distance on the 6-minute walking test at 10-20 weeks

1.3.6. Overview of efficacy endpoints

Table 1. Efficacy endpoints according to the type of variable.

Type of variable	Endpoint	Type of endpoint
TIME TO POSITIVE EVENT	Time to clinical improvement	Primary
	Time since randomization until independence from supplemental oxygen or live discharge from the hospital, whichever occurs first.	Supportive for the primary endpoint
	Time since randomization until independence from mechanical ventilation	Supportive for the primary endpoint
	Time since randomization until live hospital discharge	Supportive for the primary endpoint
	Time since randomization until absence of fever for more than 48h without antipyretics or live hospital discharge, whichever comes first	Secondary
TIME TO NEGATIVE EVENT	Time since randomization until first use of high-flow oxygen devices, non-invasive or invasive mechanical ventilation, or death	Supportive for the primary endpoint
	Time since randomization until death from all causes	Secondary
COUNT OF POSITIVE DAYS	Absolute number of invasive ventilator-free days up to 28 days after randomization	Supportive for the primary endpoint

	Absolute number of days without supplemental oxygen use up to 28 days after randomization	Supportive for the primary endpoint
	Absolute number of invasive ventilator-free days up to 28 days after randomization	Supportive for the primary endpoint
COUNT OF NEGATIVE DAYS	Absolute number of days in hospital	Supportive for the primary endpoint
	Absolute number of days in ICU	Supportive for the primary endpoint
	Absolute number of days with fever during hospital stay since randomization	Supportive for a secondary endpoint
RATE OF NEGATIVE DAYS	Relative number of invasive ventilator days, relative to number of days alive the first 28 days after randomization	Supportive for the primary endpoint
	Relative number of days in hospital, relative to number of days alive the first 28 days after randomization	Supportive for the primary endpoint
	Relative number of days in ICU, relative to number of days alive the first 28 days after randomization	Supportive for the primary endpoint
CONTINUOUS	Mean change from day 1 in PaO_2/FiO_2at day 15 or discharge, whichever comes first	Key secondary
	Mean ferritin level at day 6 (or discharge, whichever comes first)	Key secondary
	Mean SOFA score at day 6 (or discharge, whichever comes first)	Key secondary
	Mean slope of SOFA score over time	Supportive for a secondary endpoint
	Mean SOFA score at day 15 (or discharge, whichever comes first)	Supportive for a secondary endpoint
	Mean CRP at day 6 (or discharge, whichever comes first)	Exploratory
	Mean lung fibrosis score at 10-20 weeks	Descriptive
	Mean forced expiratory volume in 1 second (FEV1) at 10-20 weeks	Descriptive
	Mean forced vital capacity (FVC) at 10-20 weeks	Descriptive
	Mean functional residual capacity (FRC) at 10-20 weeks	Descriptive
	Mean residual volume (RV) at 10-20 weeks	Descriptive
	Mean diffusing capacity of the lungs for carbon monoxide (DLCO) at 10-20 weeks	Descriptive
	Mean distance on the 6-minute walking test at 10-20 weeks	Descriptive
BINARY	All-cause mortality at day 28	Supportive for a secondary endpoint
	All-cause mortality at week 10	Supportive for a secondary endpoint
ORDINAL	Score on the 6-category ordinal scale at day 15	Descriptive
	Score on the 6-category ordinal scale at 10-20 weeks	Descriptive

1.3.7. Safety endpoints

- Death
    - Time since randomization until death from any cause
    - All-cause mortality at day 28
    - All-cause mortality at week 10
- Nosocomial bacterial or invasive fungal infection within 28 days after randomization
- Sepsis during hospital stay
- Septic shock during hospital stay
- Adverse events and subclassifications thereof
    - AEs leading to death
    - AEs leading to discontinuation of study treatment
    - Suspected unexpected serious adverse reactions (SUSARs)
    - Serious adverse reactions (SARs)
    - Adverse reactions (ARs)
    - Serious adverse events (SAEs)
    - AEs not including SAEs that exceed a frequency threshold of 5%
- Laboratory parameters at day 1, day 6, and day 15 or discharge (whichever comes first)
    - Hemoglobin (g/dL)
    - Thrombocyte count (10^3 #/µL)
    - C-reactive protein, CRP (mg/L)
    - Procalcitonin (ng/mL)
    - Creatinine (mg/dL)
    - Alanine aminotransferase, ALT (IU/L)
    - Bilirubin (mg/dL)
    - Ferritin (µg/L)
    - Arterial oxygen partial pressure, PaO_2 (mmHg)
    - Fraction of inspired oxygen, FiO_2 (%)
    - D-dimers (ng/mL)
- Vital signs at day 1, day 6, and day 15 or discharge (whichever comes first)
    - Mean arterial pressure (mmHg)
    - Respiratory rate (#/min)
    - Pulse rate (#/min)
    - Highest temperature in the last 24h (°C)

2. STUDY METHODS

2.1. Trial design

- Superiority trial
- Randomized controlled 2x2 factorial design
- Non-blinded
- Multi-center (16 participating centers)

2.2. Interventions

2.2.1. IL-1 blockade treatment

2.2.1.1. Anakinra (KINERET®)

Anakinra (KINERET®) is an IL-1 inhibitor binding to the IL-1 receptor. It is indicated in Europe for treatment of rheumatoid arthritis, cryopyrin-associated periodic syndromes and Still's disease, a rare disease-causing inflammation of joints as well as rash and fever. KINERET® will be given 1x/day 100 mg subcutaneous for 28 days (or until discharge from hospital). Dose adjustment is permitted for KINERET®, in case kidney function falls below 30 ml/min glomerular filtration rate. In this case dosing frequency needs to be adjusted to 100 mg once every other day.

2.2.2. IL-6 blockade treatment

2.2.2.1. Tocilizumab (ROACTEMRA®)

Tocilizumab (ROACTEMRA®) is a humanised anti-IL6 receptor antibody approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis and giant cell arteritis. It is also licensed for the induction of the rapid reversal of cytokine release syndrome, a form of cytokine storm caused by CAR-T treatment. IL-6 is a key pro-inflammatory cytokine and an important mediator of fever and the acute phase response. Tocilizumab prevents IL-6 from binding to soluble and cell associated IL-6 receptors inhibiting signalling. ROACTEMRA® will be given via single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection 8 mg/kg (= 0.4 ml/kg) in an infusion of 100 ml NaCl 0.9% and administration over 1 hour.

2.2.2.2. Siltuximab (SYLVANT®)

Siltuximab (SYLVANT®) is a chimeric antibody neutralizing IL-6. It has been used in treatment of metastatic kidney cell tumours, prostate cancer and multicentric form of Castelman's disease. SYLVANT ® will be given via single IV infusion at a dose of 11 mg/kg given over 1 hour as an intravenous infusion in glucose 5%.

2.3. Type of trial

The COV-AID trial has a 2x2 factorial design with two main comparisons:

A. IL-1 blockade treatment versus no IL-1 blockade treatment
B. IL-6 blockade treatment versus no IL-6 blockade treatment

Evaluation of treatment effects in the two randomizations will be conducted independently. It is expected a priori that no interaction between the treatments will be identified.

Conditionally on IL-6 blockade treatment reaching statistical significance, the trial has a 2x3 factorial design. Secondary comparisons are:

C. siltuximab treatment versus no IL-6 blockade treatment
D. tocilizumab treatment versus no IL-6 blockade treatment

2.4. Randomization

2.4.1. First randomization

Patients will be randomized using permuted block randomization with varying block size stratified for center with allocation ratio 2:1 to one of the following treatment arms (in addition to usual care):

- No additional treatment (2)
- Anakinra (1)

2.4.2. Second randomization

Simultaneously, patients will be randomized using permuted block randomization with varying block size stratified for center with allocation ratio 1:1:1 to one of the following treatment arms (in addition to usual care):

- No additional treatment (1)
- Siltuximab (1)
- Tocilizumab (1)

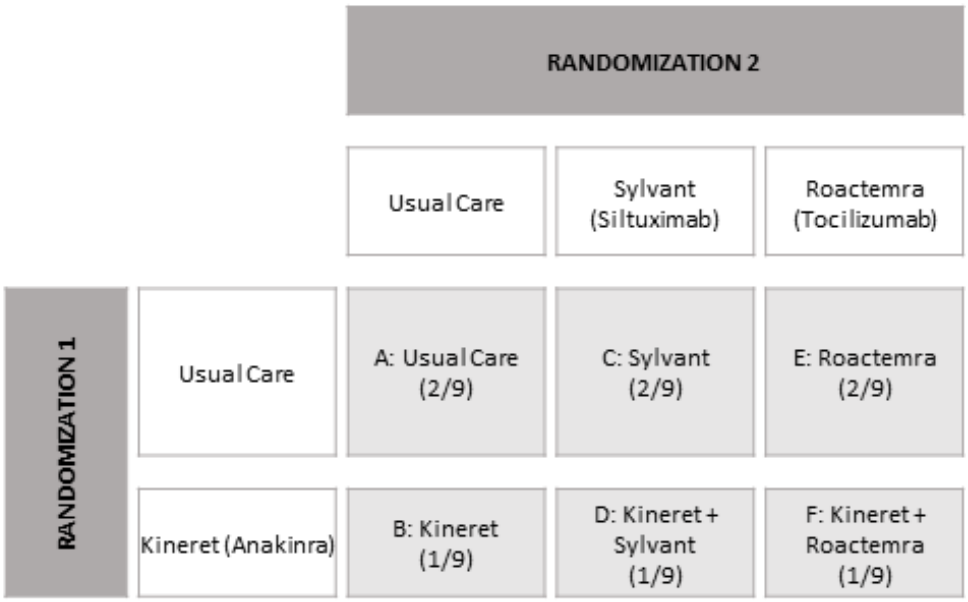


Figure 1. Schematic overview of the two randomizations.

2.5. Sample size

The study was powered to detect the two main effects of the 2x2 factorial design, assuming there is no effect modification (no interaction between the randomized treatments).

The first main effect relates to the comparison of the IL-1 blockade treatment (KINERET®) with no IL-1 blockade treatment (usual care or IL-6 blockade treatment only) (1:2). To achieve at least 80% power to detect an improvement in median time to clinical improvement from 12 days to 8 days (corresponding to a hazard ratio (HR) of 1.5) at a two-sided significance level of 5%, assuming an allocation ratio of **2:1**, we need 215 events (i.e. increase of two points on the 6-category ordinal scale or live discharge from the hospital). It was originally planned that to have an accrual period of 24 days and a follow-up period for the last patient of 28 days. Accordingly, we would need **342 patients** to observe at least 215 events, assuming 30% of patients are not susceptible to clinical improvement.

The second main effect relates to the comparison of IL-6 blockade treatment (SYLVANT® and ROACTEMRA® groups combined) with no IL-6 blockade treatment (usual care or IL-1 blockade treatment only) (2:1). To achieve at least 80% power to detect an improvement in median time to clinical improvement from 12 days to 8 days (corresponding to an HR of 1.5) at a two-sided significance level of 5%, assuming an allocation ratio of **1:2**, we need 215 events (i.e. increase of two points on the 6-category ordinal scale or live discharge from the hospital). It was originally planned to have an accrual period of 24 days and a follow-up period for the last patient of 28 days. Accordingly, 333 patients would have to be randomised to observe 215 events, assuming 30% of patients are not susceptible to clinical improvement.

The Schoenfeld approach was used to calculate the number of events. This was translated into a number of patients assuming the exponential distribution holds. Non-susceptibility was taken into account using the simple inflation method. Sample size calculations were performed using R version 3.6.1 (2019-07-05).

```
haz0 <- -log(0.50)/12
haz1 <- -log(0.50)/8
HR <- haz1/haz0
FT <- 28 # Follow-up period of last patient
AT <- 24 # Initial estimated accrual period
end <- FT + AT
p <- 1/3 # treatment allocation ratio for Anakinra
alpha <- 0.05
power <- 0.80
pi.cure <- 0.30 # Proportion of patients that "cures"
# Schoenfeld approach to calculate the number of events
d <- ceiling( ((qnorm(1-alpha/2)+qnorm(power))^2 ) / (p*(1-
p)*(log(HR))^2) )
# Translating d to N assuming the exponential distribution holds
p0 <- round(1 - ((exp(-haz0*FT)*(1-exp(-haz0*AT))) / (haz0*AT)), 3) #
event rate in the control group
p1 <- round(1 - ((exp(-haz1*FT)*(1-exp(-haz1*AT))) / (haz1*AT)), 3) #
event rate in the experimental group
ss <- ceiling(d/ (p0*(1-p) + p*p1))
# Simple inflation method to take into account 30% non-susceptibility
ass <- ceiling(ss/(1-pi.cure)/9)*9
```

As shown in the figure below, at least 215-246 events (i.e. increase of two points on the 6-category ordinal scale or live discharge from the hospital) are needed to achieve at least 80-85% power respectively to detect an improvement in median time to clinical improvement from 12 days to 8 days (corresponding to an HR of 1.5) at a two-sided significance level of 5%, with an allocation ratio of 1:2 (or 2:1).

For time to event endpoints, it is the number of events that drives the power, not the number of patients. Therefore, it is more important to observe the required number of events (clinical improvements) than to randomize the calculated needed number of patients. Hence, randomization was planned to stop either when 342 patients had been randomized or when 215-246 events (clinical improvements) had been observed, whichever came first and led to the smallest number of patients.

The actual accrual and follow-up periods were longer than originally intended. Three hundred and forty two (342) patients were randomized between April 4th and December 6th 2020, corresponding to an actual accrual period of 247 days instead of the anticipated 24 days. Follow-up was still ongoing on February 24th 2021, corresponding to a follow-up period exceeding 80 days, instead of the anticipated 28 days. Due to the longer accrual and follow-up periods, the observed number of clinical improvements is expected to exceed 215 events, leading to more than 80% power to detect a treatment effect.

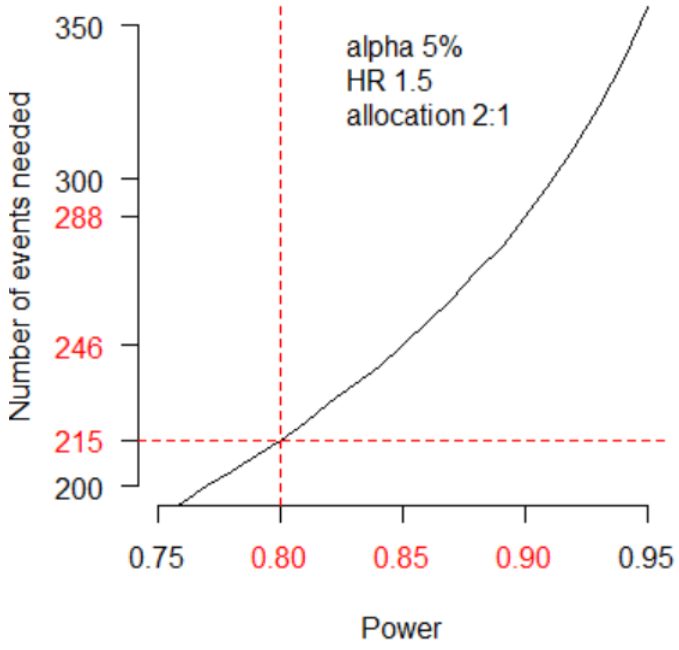


Figure 2. Number of events needed as a function of the wanted power.

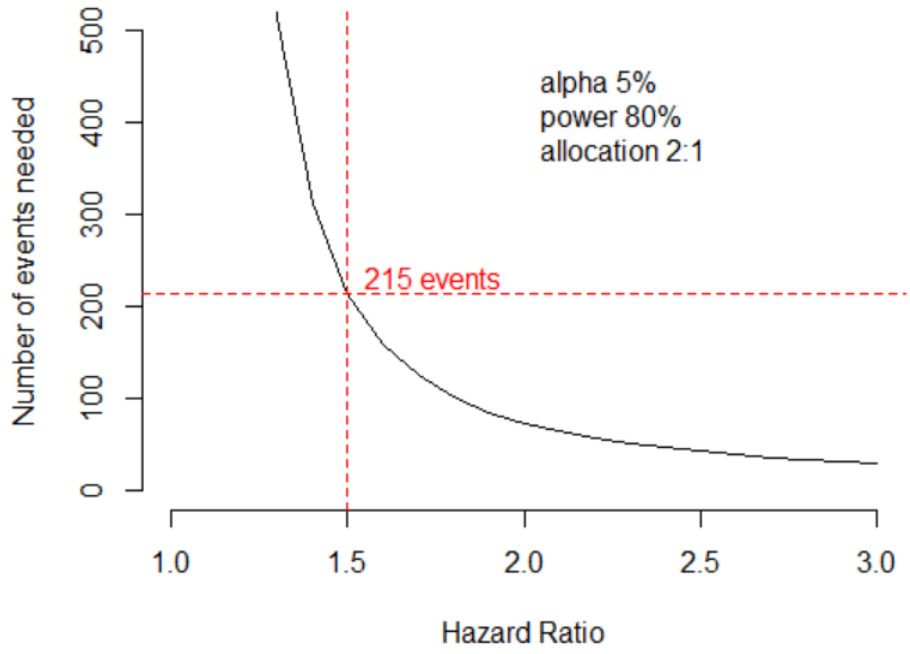


Figure 3. Number of events needed as a function of the clinically relevant hazard ratio to detect.

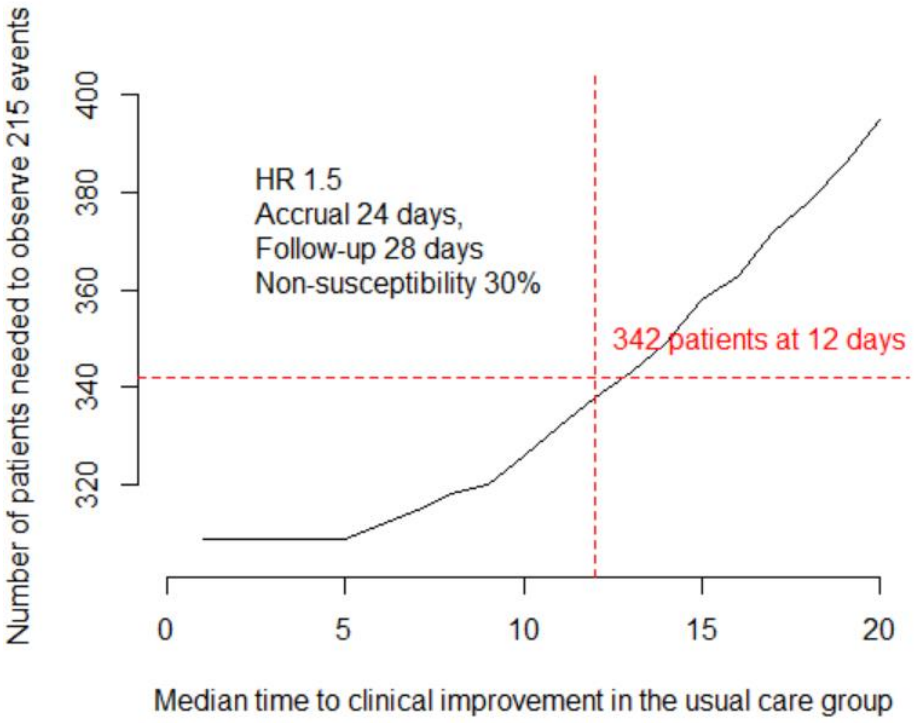


Figure 4. Number of patients needed to observe 215 events as a function of the expected median time to event in the usual care group.

2.6. Hypothesis framework

For all endpoints, the null hypothesis for the two main comparisons will be that there is no true difference in effect between any of the treatment arms.

Table 2. Overview of the hypothesis frameworks according to comparison.

Comparison	Null hypothesis	Framework
IL-1 BLOCKADE TREATMENT VS. NO IL-1 BLOCKADE TREATMENT	No true difference	Superiority
IL-6 BLOCKADE TREATMENT VS. NO IL-6 BLOCKADE TREATMENT	No true difference	Superiority
SILTUXIMAB VS. NO IL-6 BLOCKADE TREATMENT	No true difference	Superiority
TOCILIZUMAB VS. NO IL-6 BLOCKADE TREATMENT	No true difference	Superiority
SILTUXIMAB VS. TOCILIZUMAB	No equivalence	Equivalence

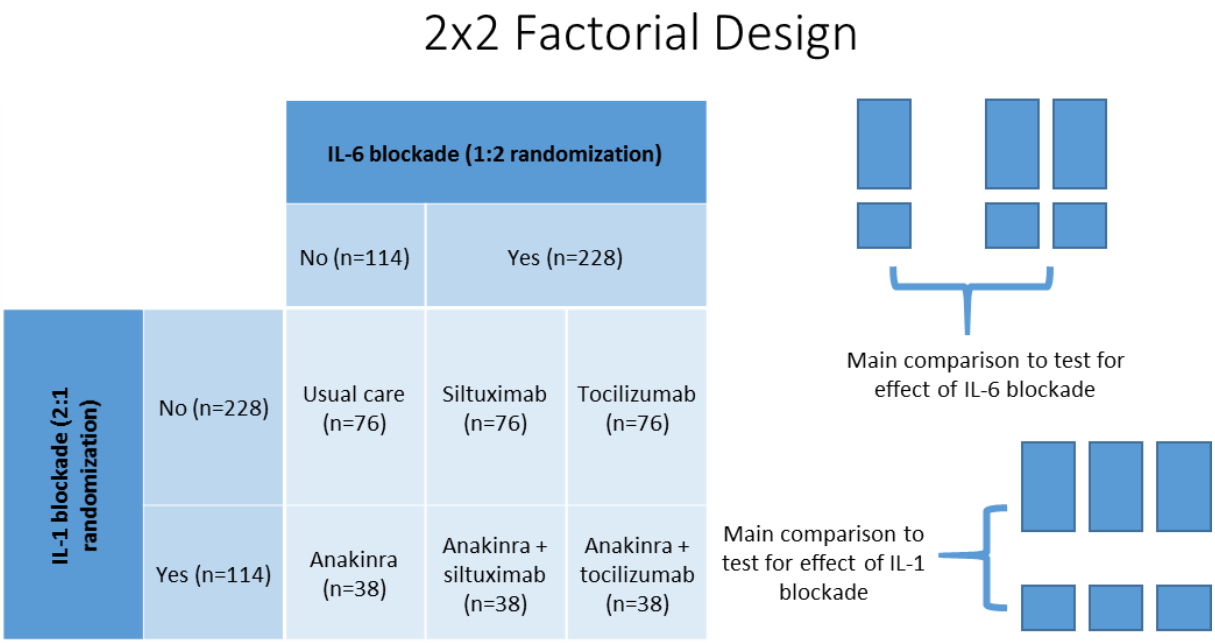


Figure 5. Overview of the 2x2 factorial design, sample size per arm and main comparisons.

2.6.1. Equivalence limits

If superiority of IL-6 blockade treatment versus no IL-6 blockade treatment can be shown and if both siltuximab and tocilizumab are shown to be superior to no IL-6 blockade treatment, only then equivalence between siltuximab and tocilizumab will be tested. Although this trial is not powered to show equivalence, equivalence will be concluded in the case where the 95% CI for the HR will entirely lie between 0.80 and 1.25. These equivalence limits are commonly used for equivalence and are approximately equal to half of the superiority effect that is used to calculate the sample size.

2.7. Interim analyses and data monitoring

Given the short estimated duration of the study (24 days for recruitment + 28 days for follow-up of the last patient), no interim analyses to stop for efficacy or futility are planned.

A Data Safety Monitoring Board (DSMB) has been foreseen to monitor covid-19 related academic trials initiated by the Ghent University Hospital. This board is independent from the COV-AID study team and has no conflict of interest with the trial's outcomes. All study medication is registered and used in current practice.

Interim analyses for safety will not affect the type I error rate and hence will not lead to adjustment of the significance level.

2.8. Timing of analyses

Final analyses will occur in separate stages. They will take place shortly after the respective data base lock.

The first data base lock will occur after the last randomized patient has been randomized for at least 28 days and after data for the relevant endpoints have been received and cleaned. During the first stage analysis, analyses will only be performed using the ITT population and will relate to:

- The primary endpoint
- Supportive endpoints related to the primary endpoint (except for clinical improvement using the 8-category ordinal scale)
- One of the secondary endpoints: Time since randomization until death from all causes
- Supportive endpoints related to this secondary endpoint: All-cause mortality at day 28
- One of the descriptive endpoints: Score on the 6-category ordinal scale at day 15
- One of the safety endpoints: sepsis or septic shock during hospital stay

In case the ITT analysis on the primary endpoint is not significant or in case IL-6 blockade treatment, siltuximab, and tocilizumab reach statistical significance on the primary endpoint, a second data base lock will occur shortly afterward the first. This second data base lock will occur when data on eligibility and treatment compliance has been cleaned. Analysis of the primary endpoint will be redone using the per protocol population to either gain more understanding or to test for equivalence between siltuximab and tocilizumab. Analysis on the ITT population will not be repeated.

The final data base lock will occur after the last randomized patient has been randomized for at least 20 weeks and after all relevant data have been received and cleaned. Analyses will be performed related to:

- Secondary endpoints and their supportive endpoints. The analysis of time since randomization until death from all causes will be repeated with longer follow-up using mortality data from the national registry if timely available. This is the only analysis from the first stage that will be repeated using again the ITT population.
- Exploratory endpoints: Mean CRP at day 6 (or discharge, whichever comes first)
- Descriptive endpoints at follow-up between 10-20 weeks post-randomization
- Safety endpoints
- Subgroup analyses on the primary endpoint according to serum IL-1 level and serum IL-6 level

2.9. Timing of assessments

All randomized participants will be followed until 10 to 20 weeks post-randomization (or death). To assess the primary endpoint, patients will be followed until the event of clinical improvement (an increase of at least 2 points on the 6-category ordinal scale from the status at randomization or live discharge from the hospital) has been observed, until death or until the cutoff date for the first data lock, whichever comes first.

We refer to a separate document concerning the definition and derivation of baseline characteristics and outcomes for more clarification on which assessments are related to the efficacy endpoints.

Table 3. Timing of assessments related to efficacy endpoints.

Assessments related to efficacy endpoints	Day of randomization	Daily until discharge	D6 or discharge	D15 or discharge	Start date	End date	Follow-up
6-category ordinal scale, worst score	x	x	x	x	NA	NA	x
Arterial blood gas assessment for PaO_2/FiO_2 ratio	x		x	x	NA	NA	x
Method of supplemental oxygen between 6-10AM	x	x	x	x		After discharge	x
Antipyretics in the last 24h	x	x	x	x	NA	NA	x
Highest temperature in the last 24h	x	x	x	x	NA	NA	x
SOFA score, evaluated between 6-10 AM, based on the worst values in the previous 24h	x		x	x	NA	NA	
Blood sampling for laboratory assessments of ferritin and CRP	x	Collected if available	x	x	NA	NA	
ICU data (including ARDS, ECMO, Glucocorticoid use)	x	x	x	x	ARDS onset, ICU admission	ICU discharge	
Survival status	x	x	x	x		Death	x
Lung function test & fibrosis score					NA	NA	x
6 minutes walking test					NA	NA	x

Table 4. Timing of assessments related to safety endpoints.

Assessments related to efficacy endpoints	Day of Randomization	Daily until discharge	D6 or discharge	D15 or discharge	Start date	End date	Follow-up
Survival status	x	x	x	x		Death	x
Nosocomial bacterial infection, invasive fungal infection	x	x	x	x			
Adverse events (including sepsis and septic shock)	x	x	x	x	AE onset	AE end	x
Vital signs (evaluated between 6-10AM during hospital stay)	x	x	x	x	NA	NA	x
Blood sampling for laboratory assessments	x		x	x	NA	NA	x

Recording of AEs starts at the time of consent. Recording of ARs starts at the time of the first dose administration. AE's are recorded until all active study subjects have completed scheduled follow up visits. AE information is collected systematically.

2.10. Blinding

This is an open-label study. While the study is in progress, access to tabular results of efficacy outcomes by treatment allocation will not be available to the research team and investigators. The DSMB and trial statistician will be unblinded for the safety outcomes.

3. STATISTICAL PRINCIPLES

3.1. Significance levels and confidence intervals

The two main comparisons of the primary efficacy endpoint will each be performed at the 5% significance level. No adjustment for multiplicity will be made, as we consider the two research questions to be independent. Interaction between IL-1 blockade treatment and IL-6 blockade treatment for the primary endpoint will be tested at the 10% significance level.

If the overall effect of IL-6 blockade treatment is statistically significant, then the individual effects of siltuximab and tocilizumab are tested, using the Hochberg procedure to control the significance level. If the largest of the two p-values for the individual effects is smaller than 5%, both null hypotheses will be rejected. Otherwise, the smallest p-value will be compared with 2.5%.

If the individual effects of both siltuximab and tocilizumab compared to no IL-6 blockade treatment on time to clinical improvement are statistically significant, then equivalence between siltuximab and tocilizumab is assessed using the 95% CI.

Table 5. Significance level and confidence interval by comparison for the primary endpoint.

Comparison	Significance level	Adjustment for multiplicity	Reported confidence interval
IL-1 blockade treatment vs. No IL-1 blockade treatment	5%	None	95%
IL-6 blockade treatment vs. No IL-6 blockade treatment	5%	None	95%
Siltuximab vs. No IL-6 blockade treatment	5% or 2.5%	Hochberg	95%
Tocilizumab vs. No IL-6 blockade treatment	5% or 2.5%	Hochberg	95%
Siltuximab vs. Tocilizumab	/	None	95%

The two main comparisons of all key secondary efficacy endpoints will be tested using the Hochberg procedure to control the type I error rate. No adjustment for multiplicity will be made for the main comparisons of other non-key secondary endpoints, because these non-key secondary endpoints are used to support the primary endpoint and/or to demonstrate additional effects and will only be interpreted if there is first a demonstration of a treatment effect on the primary endpoint.

Comparisons of exploratory endpoints and subgroup analyses will be performed at the 5% significance level, but will be interpreted cautiously.

All reported confidence intervals (CIs) for estimates of between-group effects will be 95% CIs.

3.2. Interpretation of supportive analyses

Analyses on supportive endpoints related to the primary endpoint, non-key secondary endpoints, and exploratory and descriptive endpoints will only be interpreted after efficacy on the primary endpoint can be demonstrated ($p < 0.05$). If the analysis of the primary endpoint is not significant, the analyses on non-key secondary and supportive endpoints should be considered as hypotheses-generating (not conclusive) and interpreted with care. In the latter case only estimates with 95% CIs will be provided, but no p values will be reported!

Analyses on key secondary endpoints will be corrected for multiple testing using the Hochberg procedure.

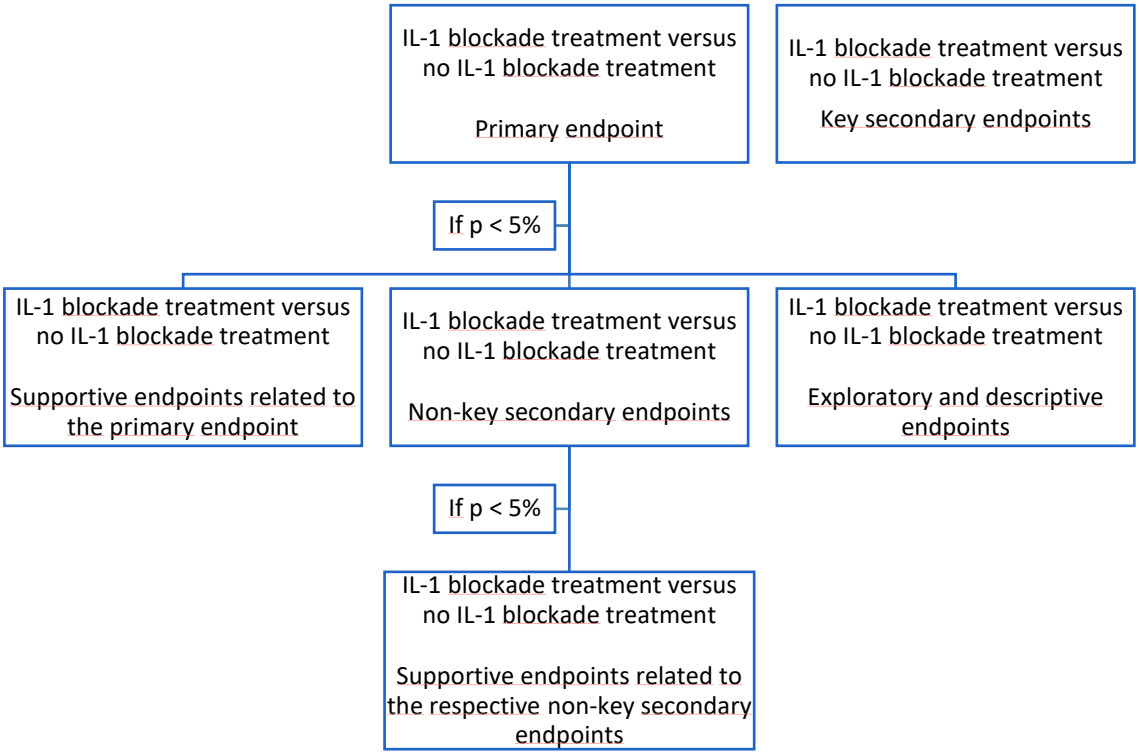


Figure 6. Direction of interpretation for the first randomization.

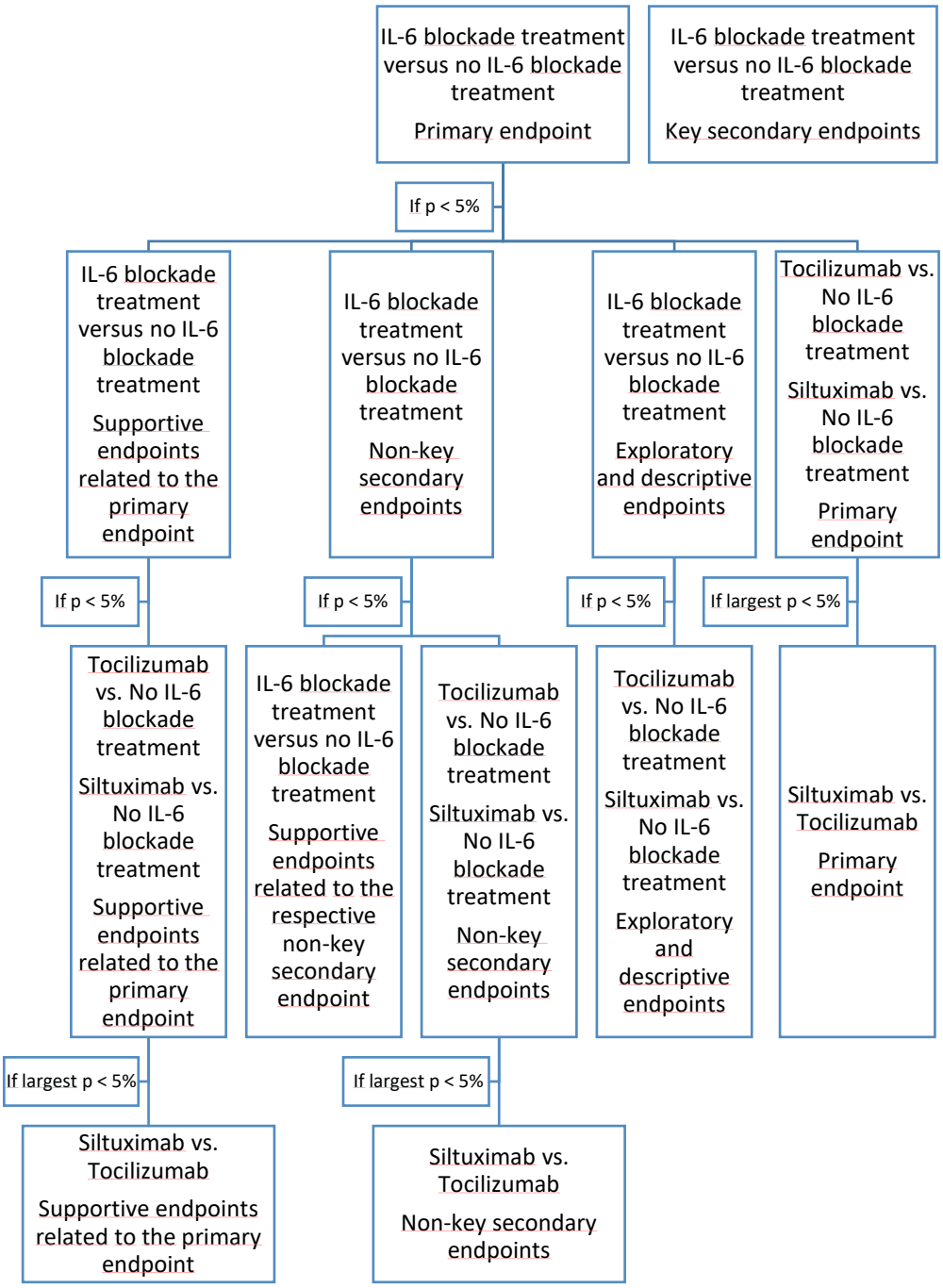


Figure 7. Direction of interpretation for the second randomization.

3.3. Protocol deviations, treatment adherence, eligibility

3.3.1. Protocol deviations

Protocol deviations concerning Informed Consent Form, Safety reporting, Eligibility, Trial assessments, Treatment deviation and others will be summarized by allocated treatment arm.

3.3.2. Treatment exposure and compliance

3.3.2.1. Anakinra

For patients allocated to any of the treatment arms with anakinra, it will be assessed daily until discharge or day 28, whichever comes first, whether or not KINERET® was administered. The reasons for missed dose(s) will be specified in text form. All patients who withdraw their consent or refuse further treatment with anakinra (KINERET®) will be considered as not compliant (regardless of how many days they have actually received anakinra). Patients who do not receive anakinra daily because of low kidney function (doctor's decision) are considered as compliant with the treatment.

3.3.2.2. Siltuximab or tocilizumab

For patients allocated to any of the treatment arms with siltuximab or tocilizumab, it will be assessed whether or not the single IV infusion with SYLVANT® or ROACTEMRA®, respectively was administered. Patients are considered compliant when they have received a single intravenous infusion of SYLVANT® or ROACTEMRA®, respectively, irrespective of the dose administered.

3.3.2.3. Reporting

The frequency of patients who did not receive the allocated study treatment will be reported by allocated treatment arm.

Exposure to anakinra treatment according to actual treatment arm will be characterized by the minimum, median and maximum duration of exposure to anakinra (days with administration).

Compliance to treatment according to actual treatment arm will be characterized by the absolute frequency of patients according to the total number of missed doses and by the absolute frequency of patients having missed at least 1 dose.

All patients with at least one missed dose will be listed by center together with the patient identifier, age, sex, actual treatment received, the number of received administrations, the number of missed administrations and information on whether an AE leading to discontinuation of study treatment occurred.

3.4. Analysis populations

3.4.1. Intent-to-treat population

The intent-to-treat population consists of all patients randomized. Subjects are analyzed according to the allocated treatment group irrespective of their compliance with the planned course of treatment. The intent-to-treat population is considered the main analysis population for analysis of efficacy data to assess superiority.

For the analysis of time to event endpoints, only patients who are still at risk for the event at day of randomization will be included in the analyses.

Table 6. Population at risk for events.

Time to event endpoint	Population at risk for the event at day of randomization
Time to clinical improvement	All randomized patients
Time since randomization until independence from supplemental oxygen or live discharge from the hospital, whichever occurs first.	All randomized patients who are dependent from supplemental oxygen at day of randomization
Time since randomization until independence from mechanical ventilation	All randomized patients who are dependent from invasive ventilation at day of randomization
Time since randomization until live hospital discharge	All randomized patients
Time since randomization until absence of fever for more than 48h without antipyretics or live hospital discharge, whichever comes first	All randomized patients with fever and/or antipyretic use at day of randomization
Time since randomization until first use of high-flow oxygen devices, non-invasive or invasive mechanical ventilation, or death	All randomized patients with a score of ≥4 on the 6-category ordinal scale at day of randomization

3.4.2. Per protocol population

The per protocol set includes the data of eligible subjects who complied with the allocated treatment sufficiently to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.

Sensitivity analyses based on the per protocol population will be performed in case the ITT analysis on the primary endpoint is not significant (to gain more understanding). The per protocol population may also be used to assess equivalence of siltuximab and tocilizumab (conditionally on IL-6 blockade treatment, siltuximab, and tocilizumab reaching statistical significance).

3.4.3. Safety population

The safety analysis set includes the available data of all subjects who were randomized and received at least one dose of study treatment. Patients will be analyzed according to the treatment which they actually received. The safety population is the main analysis population for analysis of safety data.

4. TRIAL POPULATION

4.1. Eligibility criteria

4.1.1. Inclusion criteria

- **Recent infection with COVID-19** (≥6 days of flu-like symptoms or malaise yet ≤16 days of flu-like symptoms or malaise prior to randomization).
- **Confident COVID-19 diagnosis** confirmed by antigen detection test and/or PCR and/or positive serology, or any emerging and validated diagnostic laboratory test for COVID-19 within this period.

  In some patients, it may be impossible to get a confident laboratory confirmation of COVID-19 diagnosis after 24h of hospital admission because viral load is low and/or problems with diagnostic sensitivity. In those cases, in absence of an alternative diagnosis, and with highly suspect bilateral ground glass opacities on recent (<24h) chest-CT scan (confirmed by a radiologist and pulmonary physician as probable COVID-19), and a typical clinical and chemical diagnosis with signs of cytokine release syndrome, a patient can be enrolled as probable COVID-19 infected. In all cases, this needs confirmation by later seroconversion.
- **Presence of hypoxia** defined as PaO_2/FiO_2 below 350 while breathing room air in upright position or PaO_2/FiO_2 below 280 on supplemental oxygen and immediately requiring high flow oxygen device or mechanical ventilation.
- **Signs of cytokine release syndrome** defined as ANY of the following:
  - serum ferritin concentration >1000 µg/L and rising since last 24h;
  - single ferritin above 2000 µg/L in patients requiring immediate high flow oxygen device or mechanical ventilation;
  - lymphopenia defined as <800 lymphocytes/µL and two of the following extra criteria: Ferritin > 700 µg/L and rising since last 24h / increased LDH (above 300 IU/L) and rising since last 24h / D-Dimers > 1000 ng/mL and rising since last 24h / CRP above 70 mg/L and rising since last 24h and absence of bacterial infection / if three of the above are present at admission, no need to document 24h rise.
- Chest X-ray and/or CT scan showing **bilateral infiltrates** within last 2 days.
- Admitted to **specialized COVID-19 ward** or an **ICU ward** taking care of COVID-19 patients.
- Age **≥ 18 years.**
- Male or Female.
- Women of childbearing potential must have a **negative serum pregnancy test** pre-dose on day 1. Women of childbearing potential must consistently and correctly use (during the entire treatment period and 3 months after last treatment) a highly effective method for contraception.
- Willing and able to provide **informed consent** or legal representative willing to provide informed consent.

4.1.2. Exclusion criteria

- Patients with known history of serious allergic reactions, including anaphylaxis, to any of the study medications, or any component of the product.
- **Mechanical ventilation > 24h at randomization.**
- Patient on ECMO at time of screening.
- Clinical frailty scale above 3 (This frailty score is the patient status before first symptoms of COVID-19 episode).
- Active bacterial or fungal infection.
- Unlikely to survive beyond 48h.
- Neutrophil count below 1500 cells/µL.
- Platelets below 50.000/µL.
- Patients enrolled in another investigational drug study.
- Patients on high dose systemic steroids (> 8 mg methylprednisolone or equivalent for more than 1 month) for COVID-19 unrelated disorder.
- Patients on immunosuppressant or immunomodulatory drugs.
- Patients on current anti-IL1 or anti-IL6 treatment.
- Signs of active tuberculosis.
- Serum transaminase levels >5 times upper limit of normal, unless there are clear signs of cytokine release syndrome defined by LDH >300 IU/L and ferritin >700 ng/ml.
- History of (non-iatrogenic) bowel perforation or diverticulitis.
- Pregnant or breastfeeding females (all female subjects deemed of childbearing potential by the investigator must have negative pregnancy test at screening).

4.2. CONSORT flow diagram

The flow of participants through the trial will be summarized using a CONSORT flow diagram for the two randomizations separately. The flow diagrams will summarize the number of patients who gave consent to participate and who

- were randomized
- were randomized but not eligible
- were allocated to intervention
- received allocated intervention
    - received allocated intervention and were fully compliant
    - received allocated intervention, but were not fully compliant
- did not receive allocated intervention
    - withdrew consent before receiving allocated intervention
    - other reason why the allocated intervention was not received
- completed the study until hospital discharge
- did not complete the study until hospital discharge
    - withdrew consent before hospital discharge
    - were transferred to a non-participating hospital
    - died in hospital
    - were still in hospital

  - were lost to follow-up before hospital discharge
- were included in the primary analysis on the primary endpoint
  - experienced clinical improvement
  - died before clinical improvement
  - withdrew consent before clinical improvement
  - were transferred to a non-participating hospital with loss to follow-up on the ordinal scale
  - were still in hospital without clinical improvement (administratively censored)
  - were lost to follow-up on the event for other reasons (censored)
- completed the study until follow-up at 10-20 weeks
- did not complete the study until follow-up at 10-20 weeks
  - withdrew consent
  - died
  - were readmitted to another hospital
  - were lost to follow-up for other reasons

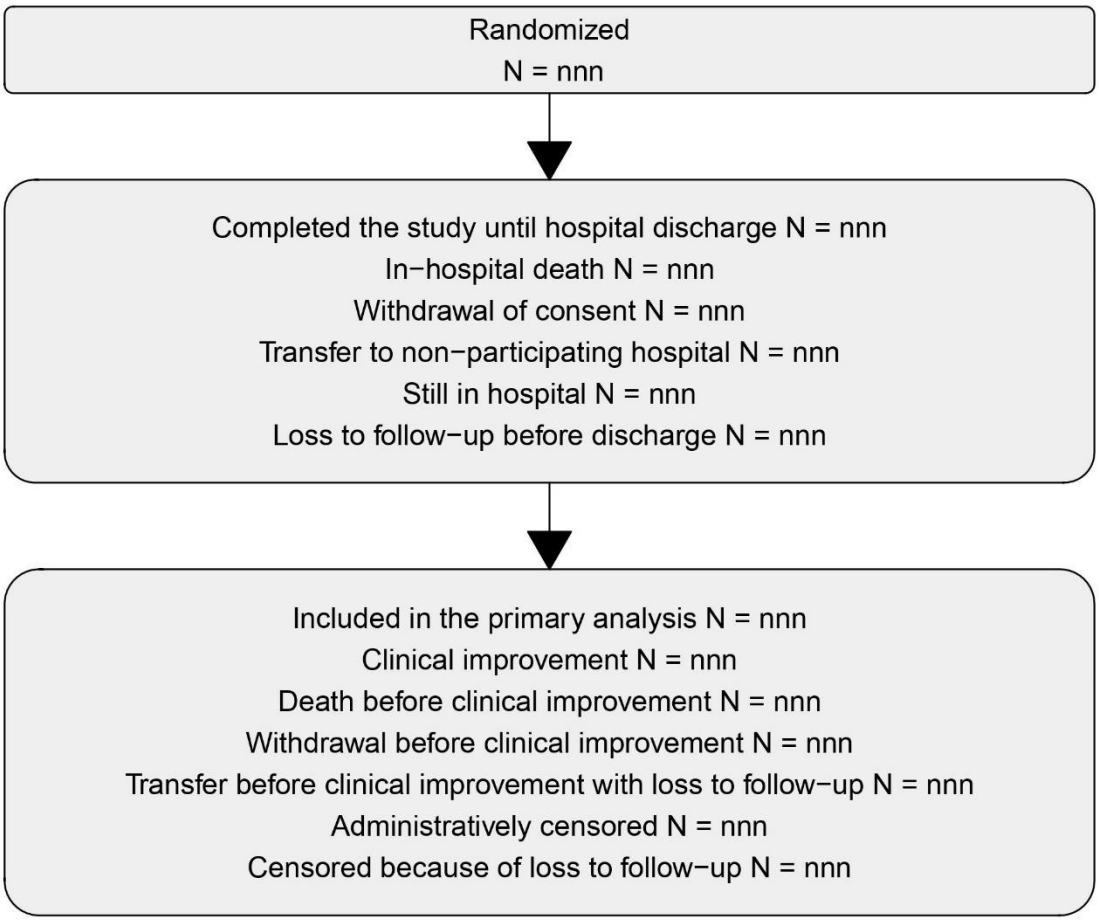


Figure 8. Blinded shell flow diagram for the first stage of the final analysis.

4.3. Baseline patient characteristics

The following characteristics will be described separately for the two randomizations according to randomized treatment (IL-1 blockade treatment vs. no IL-1 blockade treatment | siltuximab vs. tocilizumab vs. no IL-6 blockade treatment).

- Age at randomization (years)
- Gender (male, female)
- Time until randomization since COVID-19 symptoms onset (days)
- Time until randomization since hospitalization (days)
- Ethnicity (Caucasian, Asian, African, Arabian, other)
- Body mass index (kg/m²)
- Smoking status (current, former, never)
- Score on the 6-category ordinal scale at day of randomization
- Invasive ventilation at day of randomization (yes, no)
- Admission status (ward, ICU) at day of randomization
- PaO2/FiO2 ratio at day of randomization
- Aa gradient (mmHg) at day of randomization
- Comorbidities ongoing at time of informed consent (cancer, cardiovascular disease, cardiovascular risk factor, chronic kidney disease, chronic lung disease, diabetes mellitus, immunosuppression, severe liver disease, other disease)
- Medication at day of randomization (antibiotics, antiviral medication, glucocorticoids, hydroxychloroquine, or other)
- CRP (mg/L) at day of randomization
- Eosinophil count (10^3 / µL) at day of randomization
- Lymphocyte count (10^3 / µL) at day of randomization
- Ferritin (µg/L) at day of randomization
- D-dimers (µg/mL) at day of randomization
- LDH (IU/L) at day of randomization
- SOFA score at day of randomization
- Method of inclusion (Single ferritin > 2000 ng/mL in patients with High flow nasal oxygen or mechanical ventilation, Ferritin above 1000 and rising since last 24h, Lymphopenia < 800/_L and two extra criteria, Lymphopenia < 800/_L and three extra criteria)

Binary and categorical variables will be described with absolute and relative frequencies. Continuous and integer variables will be described using the mean and standard deviation or the median and the 25th – 75th percentiles, depending on the distribution. There will be no tests of statistical significance performed nor CIs calculated for differences between randomized groups on any baseline variable.

5. DEFINITION AND DERIVATION OF BASELINE CHARACTERISTICS AND OUTCOMES

This information will be included in a separate document, written by the trial statistician and reviewed by the trial data manager.

6. ANALYSIS

6.1. Analysis methods

Table 7. Analytical approach and population-level summary by type of endpoint.

Type of variable	Estimator = analytical approach	Estimate
TIME TO EVENT	Cox proportional hazards model stratified for the other randomization	Hazard ratio
COUNT	Negative binomial model adjusted for the other randomization	Expected count ratio
RATE	Negative binomial model adjusted for the other randomization with offset (log-transformed number of days alive during the first 28 days after randomization)	Expected rate ratio
CONTINUOUS	Linear regression model adjusted for the other randomization	Mean difference
BINARY	Kaplan-Meier estimates at a certain time	/
ORDINAL	Proportional odds model adjusted for the other randomization	Odds ratio of being in a less favorable category

6.1.1. Analysis methods for time to event endpoints

A summary will be given according to allocated treatment of:

- the total number of events
- the total number of censored cases (with distinction of administrative censoring, censoring due to death, censoring due to withdrawal, and censoring due to loss to follow-up)
- the median event-free survival time and 95% CI, if at least 50% of patients has reached the event of interest in each group. Otherwise, the 25th percentile or 10th percentile will be reported, if at least 25% or 10% of patients has reached the event, respectively. (obtained from the Kaplan-Meier curve)
- the probability of being event-free at day 28 (Kaplan-Meier estimate) with 95% CI
- the median follow-up time (obtained from the Kaplan-Meier curve after inverting the censoring indicator)

The survival functions will be estimated non-parametrically with the Kaplan-Meier method and compared using the log-rank test, ignoring the other randomization. The log-log approach will be used to calculate the pointwise 95% CI for the survival function. For time to negative events, the survival function will be plotted according to allocated treatment. For time to positive events, the cumulative incidence function (one minus the survival function) will be plotted according to allocated treatment. This non-parametric analysis does not take into account the other randomization.

```
PROC LIFETEST
      DATA = data_prim_analysis
      PLOTS = (survival(CL failure atrisk outside(0.15)))
      METHOD = KM CONFTYPE = LOGLOG ;
      TIME &Time*&Status(0);
      STRATA &Stratum;
RUN;
```

Cox proportional hazards models stratified for the other randomization will be fitted in order to obtain the HR and 95% Wald CI. The two-sided p-value from the Score test will be reported. This corresponds to the p-value of a stratified log-rank test. The exact method (and not Breslow's approximation) will be used for construction of the likelihood for tied event times, assuming there is a true but unknown ordering for the tied event times. Because all time to event outcomes are

expressed in days, tied event times might be common as a result of this imprecise measurement of time.

```
PROC PHREG
      DATA = data_prim_analysis;
      CLASS IL1_trt (REF = LAST) IL6_trt_bin (REF = FIRST);
      MODEL &Time*&Status(0) = IL1_trt
                        / TIES = exact RISKLIMITS;
      STRATA IL6_trt_bin;
RUN;
PROC PHREG
      DATA = data_prim_analysis;
      CLASS IL1_trt (REF = LAST) IL6_trt_bin (REF = FIRST);
      MODEL &Time*&Status(0) = IL6_trt_bin
                        / TIES = exact RISKLIMITS;
      STRATA IL1_trt;
RUN;
```

The proportional hazards assumption will be checked by visual inspection of the log-log survival curves (estimated non-parametrically with the Kaplan-Meier method).

6.1.2. Analysis methods for count and rate endpoints

Negative binomial models with a log link function adjusted for the other randomization will be fitted in order to obtain the estimated ratio of expected counts and 95% CI.

```
PROC GENMOD
      DATA = data_prim_analysis;
      CLASS IL1_trt (REF = LAST) IL6_trt_bin (REF = FIRST);
      MODEL &count = IL1_trt IL6_trt_bin
            / TYPE3 DIST = negbin LINK = log;
      LSMEANS IL1_trt / DIFF CL EXP ILINK;
      LSMEANS IL6_trt_bin / DIFF CL EXP ILINK;
RUN;
```

For some negative count endpoints, both the absolute count and the rate relative to the number of days known to be alive the first 28 days after randomization will be modelled. For the latter model the natural logarithm of the number of days alive the first 28 days after randomization will be used as offset variable.

```
PROC GENMOD
      DATA = data_prim_analysis;
      CLASS IL1_trt (REF = LAST) IL6_trt_bin (REF = FIRST);
      MODEL &count = IL1_trt IL6_trt_bin
            / OFFSET = LN_n_days_alive
            TYPE3 DIST = negbin LINK = log;
      LSMEANS IL1_trt / DIFF CL EXP ILINK;
      LSMEANS IL6_trt_bin / DIFF CL EXP ILINK;
RUN;
```

6.1.3. Analysis methods for continuous endpoints

Linear regression models with an identity link adjusted for the other randomization will be fitted in order to obtain the estimated mean difference and 95% CI. This is a complete case analysis, assuming missing data is missing completely at random.

```
PROC GENMOD
      DATA = data_prim_analysis;
      CLASS IL1_trt (REF = LAST) IL6_trt_bin (REF = FIRST)
      IL6_trt_bin (REF = FIRST);
      MODEL &continuous = IL1_trt IL6_trt_bin / TYPE3 DIST =
      normal LINK = identity;
      LSMEANS IL1_trt / CL;
      ESTIMATE 'Effect Anakinra' IL1_trt 1 -1;
      LSMEANS IL6_trt_bin / CL;
      ESTIMATE 'Effect IL-6 blockade treatment'
                  IL6_trt_bin 1 -1;

RUN;
```

As a sensitivity analysis for longitudinal endpoints, linear mixed models with a random intercept for patient will be fitted, adjusted for the other randomization, time point (categorical: day of randomization, day 6, and day 15), a two-way interaction between the first randomization and time point, and a two-way interaction between the second randomization and time point. The baseline score will be considered part of the outcome matrix. This sensitivity analysis will allow for missing outcome data to be missing at random. Mean profile plots will be presented alongside.

```
PROC MIXED
      DATA = data_longitudinal_analysis;
      CLASS subjid IL1_trt (REF = LAST) IL6_trt_bin (REF =
      FIRST) Day_cat (REF = LAST);
      MODEL &continuous = IL1_trt IL6_trt_bin Day_cat
      IL1_trt*Day_cat IL6_trt_bin*Day_cat/ S;
      RANDOM intercept / SUBJECT = subjid;
      LSMEANS IL1_trt*Day_cat / CL;
      ESTIMATE 'Effect Anakinra on delta Day 15-Baseline'
      IL1_trt*Day_cat 1 0 -1 -1 0 1 / CL;
      ESTIMATE 'Effect Anakinra on delta Day 6-Baseline'
      IL1_trt*Day_cat 0 1 -1 0 -1 1 / CL;
      ESTIMATE 'Effect Anakinra on Day 15' IL1_trt 1 -1
      IL1_trt*Day_cat 1 0 0 -1 0 0 / CL;
      ESTIMATE 'Effect Anakinra on Day 6' IL1_trt 1 -1
      IL1_trt*Day_cat 0 1 0 0 -1 0 / CL;
      LSMEANS IL6_trt_bin*Day_cat / CL;
      ESTIMATE 'Effect IL-6 blockade treatment on delta Day 15-
      Baseline' IL6_trt_bin*Day_cat 1 0 -1 -1 0 1 / CL;
      ESTIMATE 'Effect IL-6 blockade treatment  on delta Day 6-
      Baseline' IL6_trt_bin*Day_cat 0 1 -1 0 -1 1 / CL;
      ESTIMATE 'Effect IL-6 blockade treatment on Day 15'
      IL6_trt_bin 1 -1 IL6_trt_bin*Day_cat 1 0 0 -1 0 0 / CL;
      ESTIMATE 'Effect IL-6 blockade treatment on Day 6'
      IL6_trt_bin 1 -1 IL6_trt_bin*Day_cat 0 1 0 0 -1 0 / CL;
RUN;
```

6.1.4. Analysis methods for binary endpoints

The supportive binary efficacy endpoints for the COV-AID trial (all-cause mortality at day 28 and all-cause mortality at week 10) are actually time to event endpoints with a focus on a certain timing. Hence, Kaplan Meier estimates of survival (with log-log 95% CI) at day 28 and week 10 will be computed without further testing. This non-parametric analysis does not take into account the other randomization.

6.1.5. Analysis methods for ordinal endpoints

Proportional odds models adjusted for the other randomization will be fitted to estimate the odds ratio of being in a less favorable category.

```
PROC LOGISTIC
      DATA = data_prim_analysis;
      CLASS IL1_trt (REF = LAST) IL6_trt_bin (REF = FIRST) /
      PARAM = reference;
      MODEL ordinal_scale_D15orDIS = IL1_trt IL6_trt_bin / LINK
      = clogit EXPB;
      ESTIMATE 'Effect Anakinra' IL1_trt 1 -1 / CL EXP;
      ESTIMATE 'Effect IL-6 blockade treatment' IL6_trt_bin 1 -
      1 / CL EXP;
RUN;
```

6.2. Sensitivity analyses

In addition to the analyses of supportive endpoints and the sensitivity analyses for longitudinal continuous endpoints as described above, the following sensitivity analyses will be performed on the primary endpoint .

- Test for interaction between the two randomizations.

  It is important to recognize that this test generally has low power in a 2x2 trial designed to detect the main effects of IL-1 blockade treatment and IL-6 blockade treatment. However, if there is a significant interaction between IL-1 blockade treatment and IL-6 blockade treatment ($p< 0.01$), three pairwise comparisons to usual care with no additional treatment will be done (IL-1 blockade treatment alone, IL-6 blockade treatment alone, and the combination of IL-1 blockade treatment and IL-6 blockade treatment, compared to usual care with no additional treatment). No adjustment for multiple testing will be made, acknowledging that the type I error rate is no longer protected. Hence, the analyses will be considered exploratory. This sensitivity analysis will be performed regardless of whether significance for the primary analysis is reached or not.

- Analysis based on the per protocol population.

  This sensitivity analysis will be performed when the primary analysis on the ITT population is not significant, to gain more understanding. In case the primary analysis on the ITT population is significant, the per protocol population will only be used to test for equivalence of siltuximab and tocilizumab in case we get to that comparison (so conditionally on the IL-6 blockade treatment effect, siltuximab effect, and tocilizumab effect reaching statistical significance).

- Analysis stratified for age category (< 65 years versus ≥ 65 years).

  This sensitivity analysis will be performed regardless of whether significance for the primary analysis is reached or not.

6.3. Covariates

Because of the 2x2 factorial design, the main analyses are only adjusted for the other randomization. We expect no baseline differences between arms.

6.3.1. Multi-center studies

The trial will be conducted at 16 sites. Given that the number of patients (events) per center will be limited, it will be impracticable to include the center effects in the statistical models. In case not all treatments are available in all centers, patients in the control arm will only be included in a comparison if they could have been randomized to the corresponding active arm.

6.4. Subgroup analyses

Subgroup analyses will be performed to explore the uniformity of any treatment effect found overall. Heterogeneity may be identified by a significant test of the interaction term added to the statistical model in question. Although it should be noted that this test generally has low power in a trial designed to detect the main effect of treatment. Complementary, additional exploratory analyses within relevant subgroups will be performed and the results will be displayed graphically using a forest plot.

Subgroups will be made according to

- the allocated treatment for the other randomization
- CRP (mg/L) at randomization (≥ rounded median versus < rounded median)
- invasive ventilation at day of randomization (yes versus no).
- serum IL-1 level at randomization (≥ rounded median versus < rounded median)
- serum IL-6 level at randomization (≥ 30 pg/ml versus < 30 pg/ml)

Subgroup analyses will be treated as hypothesis-generating. The subgroup analyses according to serum IL-1 and IL-6 levels will be performed at a later stage.

6.5. Intercurrent events

Intercurrent events that can potentially occur after treatment initiation and may affect the interpretation or the existence of measurements associated with the study objectives are

- Death
- Live hospital discharge
- Transfer to a non-participating hospital
- Use of concomitant or rescue medication, such as dexamethasone

The table below shows the different strategies (treatment policy / composite / while on treatment) that will be used to address these different intercurrent events.

Table 8. Handling of intercurrent events.

Type of variable	Death	Live hospital discharge	Transfer to a non-participating hospital	Use of concomitant or rescue medication
TIME TO POSITIVE EVENT	If death occurs before the event: Censoring at longest observed hospital follow-up time	Part of the event (Composite strategy)	Censoring at the last date with known information about the event	Disregarded (Treatment-policy strategy)
TIME TO NEGATIVE EVENT	Part of the event (Composite strategy)	Censoring at the last date with known information about the event (this will most often be at discharge, except for time to death)	Censoring at the last date with known information about the event	Disregarded (Treatment-policy strategy)
COUNT OF POSITIVE DAYS	Days after death are not considered positive days	Days from discharge until day 28 are considered positive days	Disregarded (Treatment-policy strategy)	Disregarded (Treatment-policy strategy)
COUNT OF NEGATIVE DAYS	Rate relative to the number of days known to be alive the first 28 days after randomization	Days from discharge until day 28 are considered positive days	Disregarded (Treatment-policy strategy)	Disregarded (Treatment-policy strategy)
CONTINUOUS	Value at day of death (While-on-Treatment Strategy)	Value at day of discharge (While-on-Treatment Strategy)	Disregarded (Treatment-policy strategy)	Disregarded (Treatment-policy strategy)
BINARY	Part of the event (Composite strategy)	Disregarded (Treatment-policy strategy)	Disregarded (Treatment-policy strategy)	Disregarded (Treatment-policy strategy)
ORDINAL	Part of the endpoint (Composite strategy)	Part of the endpoint (Composite strategy)	Disregarded (Treatment-policy strategy)	Disregarded (Treatment-policy strategy)

6.5.1. Death

For time to positive event endpoints (such as time to clinical improvement), patients who die before having experienced the event will be censored at the longest observed hospital follow-up time seen in the study, as death can be seen as a competing risk. For time to negative events, patients who die before having experienced the event will be considered as having reached the event at the time of death (composite strategy).

For counts of positive days, the occurrence of death will be disregarded. For counts of negative days, both the absolute count (disregarding death) and the rate relative to the number of days known to be alive the first 28 days after randomization will be modelled. With the latter approach, patients with a small number of negative days because of early death will still have a high rate of negative days.

For binary safety endpoints other than all-cause mortality (nosocomial bacterial or invasive fungal infection within 28 days after randomization), the occurrence of death will be disregarded.

For the 6-category ordinal scale, death is included in the scale (score 1).

6.5.2. Hospital discharge

For time to positive event endpoints, patients with live discharge will be considered as having reached the event. For time to negative events (time since randomization until first use of high-flow oxygen devices, non-invasive or invasive mechanical ventilation, or death), patients with live discharge before the event has occurred will be censored at the date of live discharge. For time to death, the intercurrent event of live discharge will be disregarded.

For counts of positive days, days from discharge until day 28 are considered positive days.

For the 6-category ordinal scale, not being hospitalized is included in the scale (score 6).

6.5.3. Transfer to a non-participating hospital with loss to follow-up

When patients are transferred to a non-participating hospital, this may affect the existence of measurements associated with the study objectives. Even though efforts will be made to further collect important hospital data on these patients. For time to event endpoints, these patients will be censored at the last date with known information about the event (in case the event is not observed). When there is a complete loss to follow-up after transfer, the number of days in hospital and in ICU will be set to missing.

6.5.4. Use of concomitant or rescue medication

There are no restrictions regarding the use of concomitant or rescue medication. Use of additional treatments such as dexamethasone, will be disregarded in the analyses.

6.6. Missing data

6.6.1. Missing covariates and baseline characteristics

Missing values in covariates is not an issue since they will be no adjustment for covariates.

Missing values in the descriptive analysis of the baseline characteristics will be reported as missing.

In case eligibility criteria are missing in the eCRF, we will assume the best case scenario, being that the inclusion criterion is fulfilled.

6.6.2. Missing endpoints

The proportion of endpoints is expected to be very low, as data to derive these endpoints are typically recorded in each hospital file.

Monotone missing values will most often not be imputed, which is not fully in line with the ITT principle. Complete case analyses will assume for missing data to be missing completely at random. However, if possible given the type of data, statistical models that allow for missing outcome data to be missing at random, will be used (such as Cox proportional hazard models and generalized linear mixed models).

Table 9. Handling of missing outcome data.

Type of variable	Intermittent missing outcome data	Monotone missing outcome data (not due to death or transfer or withdrawal)
TIME TO EVENT	Last value carried forward	Censoring at the last date with known information about the event
BINARY	No imputation	No imputation (mortality at day 28 and at week 10 are analyzed as time to death)
COUNT OF POSITIVE DAYS	Best case scenario imputation (days with missing information are considered positive days)	Best case scenario imputation (days with missing information are considered positive days)
COUNT OF NEGATIVE DAYS	No imputation (days with missing information are considered positive days)	No imputation (days with missing information are considered positive days)
CONTINUOUS OR ORDINAL	No imputation Mixed models when longitudinal data are collected as sensitivity analysis	No imputation Mixed models when longitudinal data are collected as sensitivity analysis

The last value carried forward strategy will be used for intermittent missing data on events, assuming a change in clinical status is more likely to be registered than a status quo. Hence, the time to first registration of the respective event will be used as the event time. Patients without observed event during the trial duration (e.g. monotone missing data due to early drop-out, but not due to death) will be censored at the time of last follow-up on the respective event. We assume this censoring is non-informative conditional on the covariates in the model.

When data on the 6-category ordinal scale (needed to compute the primary endpoint: time to clinical improvement) is missing intermittently, it is assumed the value has not changed with respect to the last known value. Hence it is the time to the first registration of a 2-point increase on the 6-category ordinal scale that will be calculated. When data is missing monotone (before the event has been observed), the patient is censored at the last visit date with valid information on the 6-category ordinal scale.

6.6.2.1. Withdrawal

Data collected after day of withdrawal will not be used for analysis. Time to event endpoints will be censored at date of withdrawal. All count and rate endpoints will be set to missing for patients with withdrawal during hospital stay. Continuous and ordinal endpoints will be missing if they relate to a day after withdrawal.

6.6.3. Missing safety data

Safety data will not be subjected to any imputation and will be summarized on an observed case basis. Any missing information regarding an AE (with the exception of unknown onset or end date) will be queried for completion by the data managers and study monitors.

6.7. Additional exploratory analysis

Any post-hoc analysis requested by the oversight committees, a journal editor or referees will be labelled explicitly as such. Any further future analyses not specified in the analysis protocol will be exploratory in nature.

6.8. Other analyses

In selected centers, additional blood sampling (EDTA) will take place (at day 1, day 6, day 15 or discharge whichever comes first, and at follow-up) for flow cytometric analysis by the Flanders Institute of Biotechnology. Results from flow cytometric analysis of EDTA blood samples taken at day 1 may be used for additional subgroup analyses.

Local research objectives from Flanders Institute of Biotechnology are not described in this SAP.

6.9. Safety analyses

All safety variables will be summarized by actual treatment group using descriptive statistics. Statistical tests to compare differences between treatment groups regarding safety variables are not pre-specified. Ad-hoc tests may be performed to assess issues identified as clinically relevant or unexpected findings.

6.9.1. Death

A table of all anticipated and unanticipated deaths due to any cause, with the number and frequency of such events by actual treatment group will be provided as required by clinicaltrials.gov. The denominator to calculate the relative frequency will be the total population size.

The survival function will be estimated non-parametrically according to actual treatment group with the Kaplan-Meier method; the pointwise 95% CI and numbers at risk will also be presented. Kaplan-Meier estimates of failure probability at day 28 will be given according to actual treatment group for the six arms.

All deceased patients will be listed by center together with the patient identifier, age, sex, actual treatment received, date of randomization, date of death, time to death, and number of anakinra administrations.

6.9.2. Microbiology

The absolute and relative frequency of patients with a nosocomial bacterial or invasive fungal infection during hospital stay will be presented according to actual treatment received.

The absolute and relative frequency of patients with a sepsis or septic shock during hospital stay will be presented according to actual treatment received.

6.9.3. Adverse events

Considered sub-classifications of AEs are: AEs leading to death, AEs leading to discontinuation of study treatment, SUSARs, SARs, ARs, SAEs, and AEs not including SAEs that exceed a frequency threshold of 5%.

Tables of absolute and relative frequencies will be provided to summarize according to actual treatment group:

- The overall number of subjects having at least one AE or any sub-classification thereof. Each subject will only be counted once and any repetition will be ignored; the denominator will be the total population size.
- The number of subjects having at least one AE or any sub-classification thereof by body or organ system and preferred term drawn from the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Subjects with multiple AEs with different preferred terms are counted more than once.

- The total number of AEs or any sub-classification thereof. Subjects with multiple AEs are counted more than once.
- The number of subjects having at least one SAE by body or organ system, preferred term, grade, and relationship to study treatment (Not related or Unlikely versus Possibly, Probably or Definitely). Subjects with multiple SAEs with different preferred term are counted more than once. The most severe occurrence of a SAE, as well as the most extreme relationship of the SAE to the study procedures, will be indicated in cases of multiple occurrences of the same preferred term.

Listings by patient will be provided for: all AEs leading to death, all AEs leading to discontinuation of study treatment, all AEs of sepsis, all SAEs, and all AEs. All of the above events (including the same event on several occasions) are listed for each patient by center together with the patient identifier, age, sex, actual treatment received, and the collected information regarding the AE as described above in this subsection.

6.9.4. Clinical laboratory evaluations

- Laboratory tests for hemoglobin, thrombocyte count, C-reactive protein, procalcitonin, creatinine, alanine aminotransferase, bilirubin, ferritin, PaO_2, FiO_2, and D-dimers are summarized at day 1, at day 6 and at day 15 or the day of discharge (whichever comes first) using boxplots by received treatment.
- Changes in lab values from day 1 at day 6 and at day 15 or the day of discharge (whichever comes first) are displayed using boxplots by received treatment.
- Spaghetti plots show the individual lab values over time and are plotted separately according to received treatment.

6.9.5. Vital signs

- Vital signs (mean arterial pressure, respiratory rate, pulse rate, highest temperature in the last 24h) are summarized at day 1, at day 6 and at day 15 or the day of discharge (whichever comes first) using boxplots by received treatment.
- Changes in values from day 1 at day 6 and at day 15 or the day of discharge (whichever comes first) are displayed using boxplots by received treatment.
- Spaghetti plots show the individual values over time and are plotted separately according to received treatment.

6.9.6. Pregnancies

Pregnancies should not occur, as pregnant females are excluded from the study and all female subjects deemed of childbearing potential by the investigator must have a negative pregnancy test at screening. Pregnancies will be recorded as AE (CTCAE code PRE003).

6.10. Statistical software

The statistical software SAS version 9.4, R version 4.0.2. (2020-06-22), RStudio Version 1.3.1093 and IBM® SPSS® Statistics version 27 (or later) will be used for the analyses. All software is available on Athena from Ghent University.

6.11. Quality assurance of statistical programming

All data, code and output documents will be saved on a shared network drive from Ghent University for the Biostatistics Unit of the Faculty of Medicine and Health Sciences. ("S:\cel\Projecten\L\Lambrecht Bart\COV AID")

A review statistician (Roos Colman) will have an overview of the entire analysis and will independently from the trial statistician (Stefanie De Buyser) compute the code for derivation of the primary endpoint and for the primary analyses.

7. ADMINISTRATIVE INFORMATION

7.1. SAP revision history

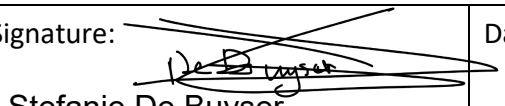
Version	Date	Edited by	Comments / justification	Timing in relation to safety interim analyses	Timing in relation to unblinding for the final analyses
0.1	11/01/2021	SDB	First draft	Post	Prior
0.2	21/01/2021	SDB	Second draft after meeting with the COV-AID team	Post	Prior
0.3	24/02/2021	SDB	Third draft after feedback from the steering committee statisticians and data manager	Post	Prior
0.4	04/03/2021	SDB	Forth draft after feedback from the steering committee statisticians, data manager and clinicians	Post	Prior
0.5	05/03/2021	SDB	Fifth draft	Post	Prior
1.0	05/03/2021	SDB	Final clean version	Post	Prior

7.2. Differences from protocol v5.0

- Patient who do not have experienced clinical improvement and do not die, will be censored at the date of their last registered day in hospital with follow-up on the ordinal scale, this does not necessarily correspond to the date of the last follow-up visit (the latter is mentioned in the protocol v5.0).
- The supportive endpoint: Absolute number of days in hospital in patients with live hospital discharge has been deleted. This endpoint will be examined in the total sample, irrespective of death.
- The Cox proportional hazard analyses will not be stratified according to dexamethasone use (as usual care in the treatment of covid19 has changed over time).
- Time since randomization until first use of salvage systemic steroids in ventilated patients (at time of randomization) has been deleted as a supportive endpoint for the primary endpoint, as systemic steroids have become part of standard care in covid19 patients.
- The comparisons of siltuximab treatment versus no IL-6 blockade treatment, tocilizumab treatment versus no IL-6 blockade treatment, and siltuximab versus tocilizumab with respect to secondary endpoints were added to the secondary objectives related to secondary endpoints.
- The endpoint all-cause mortality at week 20 has been changed to all-cause mortality at week 10. The visit window for follow-up is between week 10 and 20 post-randomization, so hardly anyone will have a follow-up of 20 weeks or more.
- Some supportive endpoints will be assessed in the entire analysis population instead of just in invasively ventilated patients: Relative number of invasive ventilator days, relative to number of days alive the first 28 days after randomization, Absolute number of days in ICU at day of randomization, Relative number of days in ICU, relative to number of days alive the first 28 days after randomization
- Subgroup analyses according to CRP and ventilation status at day of randomization are added as exploratory objectives
- Triglycerides (mg/dL) should not be assessed at day 6, day 15 or discharge, according to the protocol. Therefore, this safety endpoint has been deleted.
- The supportive endpoint “Time since randomization until first use of high-flow oxygen devices, non-invasive or invasive mechanical ventilation, ARDS or death” has been changed to “Time since randomization until first use of high-flow oxygen devices, non-invasive or invasive mechanical ventilation, or death” (removal of ARDS), because ARDS by definition cannot occur in patients without ventilation.
- Safety endpoints have been added: sepsis and septic shock during hospital stay.

7.3. Approval

I give my approval for the attached SAP.

Trial Statistician SAP author	Name: Dr. Stefanie De Buyser	
	Signature:  Stefanie De Buyser	Date: 05/03/2021
Chief Investigator	Name: Prof. dr. Bart Lambrecht	
	Signature:	Date:
Steering Committee Statistician	Name: Roos Colman	
	Signature:	Date:
Steering Committee Statistician	Name: Prof. dr. Marc Buyse	
	Signature:	Date:
Steering Committee Statistician	Name: Prof. dr. Catherine Legrand	
	Signature:	Date:

8. REFERENCES

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7.3. Approval

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Trial Statistician SAP author	Name: Dr. Stefanie De Buyser	
	Signature:	Date:
Chief Investigator	Name: Prof. dr. Bart Lambrecht	
	Signature:	Date:
Steering Committee Statistician	Name: Roos Colman	
	Signature:	Date:
Steering Committee Statistician	Name: Prof. dr. Marc Buyse	
	Signature: L. Buyse	Date: 5/3/2021
Steering Committee Statistician	Name: Prof. dr. Catherine Legrand	
	Signature: Legrand	Date: 6/3/2021

7.3. Approval

I give my approval for the attached SAP.

Trial Statistician SAP author	Name: Dr. Stefanie De Buyser	
	Signature:	Date:
Chief Investigator	Name: Prof. dr. Bart Lambrecht	
	Signature:	Date: 06/03/2021
Steering Committee Statistician	Name: Roos Colman	
	Signature:	Date: 05/03/2021
Steering Committee Statistician	Name: Prof. dr. Marc Buyse	
	Signature:	Date:
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