A phase 2/3, randomized, open-label, parallel group, 3-arm, multicenter study investigating the efficacy and safety of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, and anakinra, an interleukin-1(IL-1) receptor antagonist, versus standard of care, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection.

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Type of Study: Phase 2/3

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Signature Date

Investigator statement

I have read the protocol entitled "A phase 2/3, randomized, open-label, parallel group, 3-arm, multicenter study investigating the efficacy and safety of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, and anakinra, an interleukin-1(IL-1) receptor antagonist, versus standard of care, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection." and the accompanying current Investigator´s Brochure for emapalumab and Summary of Product Characteristics for anakinra. I agree to conduct the clinical investigation in compliance with the Final Protocol Version 3.0, 20 March 2020, the International Council for Harmonisation (ICH) harmonised guideline E6(R2): Guideline for Good Clinical Practice (GCP) [1], applicable regulatory/government regulations, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki [2]. It should be noted that due to the urgency of the situation, the Sponsor has for this protocol requested exemptions to what is required for a Clinical Trial Application and when conducting a clinical trial.

I will not implement any changes to study procedures or conduct without prior approval from the Sponsor and, when applicable, the Independent Ethics Committee and Regulatory Authority. I will supervise any individual or party to whom I delegate study-related duties and functions conducted at the study site and ensure qualification of individuals or parties who perform delegated tasks.

I agree to maintain the confidentiality of this study protocol, as described on the title page. Further, I will not publish results of the study without authorization from Swedish Orphan Biovitrum AB.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

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Synopsis

STUDY IDENTIFIERS	
Title of study:	A phase 2/3, randomized, open-label, parallel group, 3-arm, multicenter study investigating the efficacy and safety of intravenous administrations of emapalumab, an anti-interferon gamma (anti-IFNγ) monoclonal antibody, and anakinra, an interleukin-1(IL-1) receptor antagonist, versus standard of care, in reducing hyper-inflammation and respiratory distress in patients with SARS-CoV-2 infection.
Clinical study number:	Sobi.IMMUNO-101
Sponsor	Swedish Orphan Biovitrum AB, Stockholm, Sweden
Study sites	Multi-center study, 3 to 5 sites will participate in the study.
Type of study:	Phase 2/3
STUDY RATIONALE	As shown by the data available in the most recent literature generated from the Chinese experience, and by the most recent data made available by the different Italian hospitals responsible for the management of these patients, hyper-inflammation, caused by a cytokine storm resulting from an exaggerated response of the immune system to the presence of the virus, is considered to represent one of the most important negative prognostic factor in patients infected with SARS-CoV-2. The inclusion criteria for hyperinflammation used in this protocol is based on the analysis of routine blood chemistry data obtained from patients with SARS-CoV-2 infection. This criterion has been designed with high sensitivity (>90%) for patients who require ICU admission. This constitute the rationale for testing drugs specifically targeted to reduce the cytokine storm. This protocol has been prepared on the basis to address the current medical emergency, given the severity of the disease and the extremely high number of individuals affected. The objective of this study is to investigate new possibilities to reduce the number of patients requiring mechanical ventilation. This is intended to address the most urgent need to preserve the access to intense care unit support to the lower possible number of patients and may potentially reduce mortality.
STUDY OBJECTIVES	
Primary objective:	The primary objective of this study is to assess the effect of emapalumab and anakinra on hyperinflammation and pulmonary function in patients with SARS-CoV-2 infection.
Secondary objective(s):	The secondary objective of this study is to evaluate the safety and tolerability profile of intravenous (i.v.) administrations of emapalumab and anakinra in patients with SARS-CoV-2 infection.
Exploratory objective(s):	An exploratory objective of this study is to assess the effect of anakinra and emapalumab on CXCL9, IL-1, IL-6, sIL-2R and selected biomarkers relevant for hyperinflammation, whenever possible.
STUDY ENDPOINTS	
Primary endpoint:	The primary endpoint is treatment success, defined as not requiring any of the following by Day 15: • Invasive mechanical ventilation or • Extracorporeal membrane oxygenation (ECMO).

Secondary endpoints supporting the primary objective:	• Time to mechanical ventilation.
	• Change from baseline in MEWs score.
	• Change from baseline in resting SpO_2.
	• Change from baseline in PaO_2/FiO_2.
	• Change from baseline in hemogasanalysis.
	• Change from baseline in oxygen supplementation.
	• Amelioration of the findings of high-resolution CT scan of the chest.
	• Change from baseline in hyperinflammatory parameters during treatment until Day 15 with measurements performed every 3 days:
	  • Ferritin
	  • LDH
	  • D-dimers
	• Change from baseline in other relevant laboratory parameters during treatment until Day 15 with measurements performed every 3 days:
	  • WBC with differential counts
	  • RBC
	  • Hb
	  • Platelet count
	  • Fibrinogen
	  • Complement C3/C4
	  • Prothrombin time
	  • Cardiac troponin
	  • Liver tests (AST, ALT, total bilirubin levels)
	  • CRP
	  • Creatinine
	• Overall survival.
	• Time to hospital discharge.

Secondary endpoint	Safety endpoints of this study are:
	• Treatment-emergent severe fatal and life-threatening serious adverse events (SAEs).
	• Adverse events leading to premature discontinuation of study treatment.
	• Anaphylactic/anaphylactoid reactions.
	• Treatment emergent adverse events of special interest:
	  • Emapalumab treatment group: Infections caused by pathogens potentially favored by IFN-γ neutralizations such as mycobacteria, salmonella, shigella, herpes zoster and histoplasma capsulatum, and severe infusion-related reactions.
	  • Anakinra treatment group: Severe neutropenia.
	• Treatment-emergent laboratory abnormalities.

Exploratory endpoint(s):	Change from baseline in CXCL9, IL-1, IL-6, sIL-2R and selected biomarkers relevant for hyperinflammation.

STUDY DESIGN AND METHODS

Study design:

This is a randomized, open-label, parallel group, 3-arm multicenter study to investigate the efficacy and safety of emapalumab and anakinra in reducing hyper-inflammation and respiratory distress in adult patients with a documented SARS-CoV-2 infection.

The study consists of screening, a 2-week treatment period and an 8-week follow-up period.

The 2-week treatment period is open, and the patients will be randomized to treatment with emapalumab, anakinra or standard of care in a 1:1:1 ratio. Emapalumab will be administered as i.v. infusions every 3rd day for a total of 5 infusions (Days 1, 4, 7, 10, 13). Anakinra will be administered as 4-times daily i.v. infustions for 15 days (Days 1 to 15). The primary endpoint will be evaluated at Day 15.

A follow-up by visit or phone call will be performed 4 and 8 weeks after the end of the treatment period (Weeks 6 and 10).

The study duration for an individual patient will not exceed 10 weeks. The end of the study is defined as last patient last follow-up visit/phone call.

The study design has a total sample size of 54 patients and consists of two stages. At the end of Stage 1, the success rates are compared between each of the two treatment arms and standard of care and there is the potential to stop for futility or for efficacy of emapalumab or anakinra.

A data review committee composed of experts in intensive care, inflammation, infection diseases will be involved in study oversight and interpretation of the study results.

In patients showing worsening of clinical condition, independently of the treatment arm, the Investigator is completely free to decide to introduce any drug considered necessary for a given patient as rescue treatment.

Number of subjects planned:

The study will enroll a total of 54 patients, 18 per arm according to the 1:1:1 randomization

Diagnosis and main criteria for inclusion:

Patients with documented SARS-CoV-2 infection, age > 30 to < 80 years with respiratory distress and hyperinflammation.

Assessments:

The clinical and laboratory parameters to be collected at given time points are indicated in the simplified Schedule of Events presented in the end of the synopsis. This schedule also includes information on the patient´s demographics, medical history and prior medication.

Test product; dose and mode and duration of administration:

The patients will receive investigational medicinal products (IMP) according to the randomization schedule and table below.

Arm	**IMP**	**Route**	**Daily dose**	**Dosage regimen**
A	Ema-palumab	i.v. infusion	Day 1: 6 mg/kg Days 4, 7, 10, 13: 3 mg/kg	Every 3rd day for in total 5 infusions
B	Ana-kinra	i.v. infusion	Days 1-15: 400 mg/day in total, divided into 4 doses given every 6 hours	4 times daily for 15 days
C	None	N/A	N/A	N/A

Background Therapy:

All patients participating in the study will receive background therapy with methylprednisolone. In case a patient is not already receiving methylprednisolone, treatment will be initated at the time of the first study drug

administration (Day 1). In case the patient is already receiving glucocorticoids, independently of the type of glucocorticoids and the dose previously administered, the patient will receive methylprednisolone at the dose of 20 mg 3 times per day from Day 1.

Methylprednisolone will be administered according to the following dosing schedule

Study Day	Dose and dosage regimen
Days 1-5	20 mg of methylprednisolone 3 times per day i.e., 60 mg/day
Days 6-10	10 mg of methylprednisolone 3 times per day i.e., 30 mg/day
Days 11-14	5 mg of methylprednisolone 3 times per day i.e., 15 mg/day

Concomitant Therapy:

Concomitant use of IL-6 inhibitors (e.g., tocilizumab), non-anakinra IL-1 inhibitors (e.g, canakinumab), TNF inhibitors, JAK inhibitors and hydroxychloroquine is not allowed. If any of these therapies are initiated at the discretion of the Investigator e.g., as rescue therapy due to worsening of the patient's condition, then the patient should be withdrawn from study.

Antimicrobial therapy and prophylaxis are not limited.

Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, i.v. parenteral nutrition, inotropic support, antibiotics, anti-fungal and anti-viral treatments, ultrafiltration or hemodialysis, as well as general supportive care are permitted

Determination of sample size:

The study will enroll a total of 54 patients, 18 per arm according to the 1:1:1 randomization.

The sample size has been estimated based on the following assumptions:

- An overall one-sided significance level for efficacy of 0.097 (9.7%) and a power of 74% for each comparison under the assumption that the true success rates are 50% in the SoC group increasing to 80% in the emapalumab or anakinra groups.
- The study will consist of two stages, with equal numbers of patients randomised into Stage 1 and into Stage 2 per treatment arm.
- There is the potential to stop for futility or for efficacy of emapalumab or anakinra (or both) at the end of Stage 1.
- The futility rule for stopping at the end of Stage 1 is binding.

More specifically:

- The emapalumab or anakinra arm (or both) will be stopped at the end of Stage 1 for futility if the one-sided p-value in favour of emapalumab/anakinra is > 0.690.
- The emapalumab or anakinra arm (or both) will be stopped for efficacy at the end of Stage 1 if the one-sided p-value in favour of emapalumab/anakinra is < 0.025.

If the trial continues to Stage 2, efficacy will be declared at the end of Stage 2 if the one-sided p-value in favour of emapalumab/anakinra is < 0.159.

Statistical methods:

For the analysis of the primary endpoint, each of the pairwise comparisons, emapalumab/anakinra versus standard of care, at both the end of Stage 1 and at the end of Stage 2, will be undertaken using Fishers Exact test comparing the proportion of patients with treatment success. The p-value calculations will be supplemented by the presentation of one-sided exact confidence intervals.

Analysis of the time to mechanical ventilation, overall survival, and time to hospital discharge, respectively, will be undertaken by plotting Kaplan-Meier curves for each of the 3 treatment groups and by pairwise comparisons (emapalumab/anakinra versus standard of care) using the logrank test. Hazard ratios will be estimated using the Cox proportional hazards model and these will be presented together with 90% two-sided confidence intervals.

Change from baseline in MEWs score at Day 15 will be analysed using analysis of covariance (ANCOVA) including treatment arm as a fixed factor and baseline MEWs score as a covariate. Least square mean change per group, associated 90% two-sided CI, and p-values for the comparison vs. standard of care, will be presented.

Schedule of Event (for a detailed version, please refer to Section 5.5.1.1)									
ASSESSMENT	**SCREENING**	**TREATMENT PERIOD**						**FOLLOW-UP PERIOD**	
	Up to 72h prior to Visit 1	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/TC**	**Visit 8/TC**
		Day 1 (Baseline)	Day 4	Day 7	Day 10	Day 13	Day 15 (± 1 day)	Week 6 (± 5 days)	Week 10 (± 5 days)
Informed consent	X								
Eligibility criteria	X	X							
Patient information	X								
Physical examination	X								
Vital signs assessment	X	X	X	X	X	X	X		
ECG assessment	X						X		
HRCT scan of chest	X						X		
Laboratory assessments (local)	X	X	X	X	X	X	X		
Urine pregnancy test	X						X		
Randomization		X							
IMP administration		X----------X							
Concomitant medication incl background therapy		X	X	X	X	X	X		
Pulmonary function		X	X	X	X	X	X		
PaO_2/FiO_2	X						X		
Resting SpO_2 (3 times per day)		X	X	X	X	X	X		
Hemogasanalysis		X	X	X	X	X	X		
Oxygen supplementation		X	X	X	X	X	X		
MEWS score		X					X		
Survival								X	X
Time to hospital discharge								X	X
Adverse events		X	X	X	X	X	X		
Biomarkers		X	X	X	X	X	X		

Abbreviations: CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; HRCT, high resolution computed tomography; IMP, Investigational Medicinal Product; MEWS, modified early warning system; PaO_2, partial pressure of oxygen; SpO_2, peripheral capillary oxygen saturation

1 Abbreviations and definition of terms

1.1 List of abbreviations and definitions

Term	Definition
AE	Adverse event
AIFA	The Italian national competent authority
AOSD	Adult onset Still's disease
AST	aspartate aminotransferase
ALT	Alanine aminotransferase
Baseline	Before study drug administration at Visit 1 (Day 1)
CAPS	Cryopyrin-associated periodic syndrome
CDASH	Clinical data acquisition standards harmonization
CDISC	Clinical data interchange standards consortium
CPAP	Continuous positive airway pressure
CRO	Contract research organization
CRF	Case report form
CRP	C-reactive protein
CT	Computed tomography
CXCL9	Chemokine (C-X-C Motif) ligand 9
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
FiO_2	Fraction of inspired oxygen
GCP	Good clinical practice
Hb	Hemoglobin
HLH	hemophagocytic lymphohistiocytosis
pHLH	Primary hemophagocytic lymphohistiocytosis
sHLH	Secondary hemophagocytic lymphohistiocytosis
ICH	International council for harmonisation
IEC	Independent ethics committee

IL	Interleukin
IL-1Ra	Interleukin 1 receptor antagonist
IMP	Investigational medicinal product
IFNγ	Inteferon gamma
IRS	Interactive response system
i.v.	Intravenous
LDH	Lactate dehydrogenase
MAS	Macrophage activation syndrome
MedDRA	Medical dictionary for regulatory activities
MEW score	The modified early warning score
NOMID	Neonatal-onset multisystem inflammatory disease
NYHA	New York heart association
PaO_2	Partial pressure of oxygen
PLT	Platelets
RA	Rheumatoid arthritis
RR	Respiratory rate
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
s.c.	Subcutaneous
SJIA	Systemic juvenile idiopathic arthritis
Sobi	Swedish Orphan Biovitrum AB (publ)
SoC	Standard of care
SOP	Standard operating procedure
SpO_2	Peripheral capillary oxygen saturation
SRC	Safety review committee
SUSAR	Suspected unexpected serious adverse reaction
RBC	Red blood cells
TB	Tuberculosis
TNF	Tumor necrosis factor
WBC	White blood cells

2 Ethics

2.1 Independent ethics committee

It is the responsibility of the investigator to obtain approval of the study protocol, possible amendments and the written subject information and informed consent form from the IEC.The investigator should file all correspondence with the IEC. Copies of IEC correspondence and approvals should be forwarded to Swedish Orphan Biovitrum (Sobi).

2.2 Ethical conduct of the study

This study will be conducted in compliance with this protocol, the ICH GCP [1], applicable regulatory requirements, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki) [2].

It should be noted that due to the urgency of the situation the Sponsor has for this protocol requested exemptions to what is required for a Clinical Trial Application and when conducting a clinical trial (see Appendix 3).

2.3 Patient information and consent

It is the responsibility of the investigator to give each patient (or the patient's acceptable representative) prior to any study-related activities, full and adequate verbal and written information regarding the objective and procedures of the study and the possible risks involved. The patients must be informed about their right to withdraw from the study at any time. The written patient information and/or informed consent form must not be changed without prior discussion with Sobi. Before any revisions are implemented, the revised written patient information and/or informed consent form must be approved by the IEC.

It is the responsibility of the investigator to obtain signed informed consent (or witnessed verbal consent according to applicable regulations) from all patients prior to any study-related activities. The patients should receive a copy of the written information and the signed informed consent form.

3 Introduction

3.1 Background

This protocol has been prepared in response to the request formulated by Prof. Franco Locatelli (current President of the Italian Consiglio Superiore di Sanità and member of the Scientific Committee of the Italian Civil Protection, previously serving as Principal Investigator for the European development of emapalumab in children with primary HLH), and the Scientific

Director of the National Institute for Infectious Diseases (INMI) Lazzaro Spallanzani, Prof. Giuseppe Ippolito. INMI is the only IRCCS (national institute for research and care of the Italian Ministry of Health) fully devoted to Infectious disease and as WHO-CC for diagnosis, research, care and training against highly infectious diseases. Both are members of the Scientific Committee of the Italian Civil Protection and are working in strict collaboration with the Italian national competent authority (AIFA) and are committed to investigate, among others, the use of emapalumab and anakinra, in patients suffering from the SARS-CoV-2 infection and experiencing respiratory distress.

For the preparation of this protocol, expertize in hyperinflammation, in the treatment of cytokine release syndromes, and in the treatment of infection diseases, has been provided by Franco Locatelli, Fabrizio De Benedetti and Giuseppe Ippolito, together with contribution of the many physicians currently involved in the treatment of patients infected with SARS-CoV-2 in Italy.

The objective of this study is to investigate new possibilities to reduce the number of patients requiring mechanical ventilation. This is intended to address the most urgent need to preserve the access to intense care unit support to the lower possible number of patients and may potentially reduce mortality.

3.2 Study rationale

As shown by the data available in the most recent literature generated from the Chinese experience [4, 5, and 6], and by the most recent data made available by the different Italian hospitals responsible for the management of these patients (unpublished data generated in the laboratory of Immunology of the National Institute for Infectious Diseases and the Laboratory of ImmunoRheumatology of the Ospedale Pediatrico Bambino Gesù), hyper-inflammation, caused by a cytokine storm resulting from an exaggerated response of the immune system to the presence of the virus, is considered to represent one of the most important negative prognostic factor in patients infected with SARS-CoV-2. The inclusion criteria for hyperinflammation used in this protocol is based on the analysis of routine blood chemistry data obtained from patients with SARS-CoV-2 infection. This criterion has been designed with high sensitivity (>90%) for patients who require ICU admission. This constitute the rationale for testing drugs specifically targeted to reduce the cytokine storm.

3.3 Potential risks and benefits

Anakinra is a recombinant form of the human IL-Ra, r-metHuIL-1Ra, which is produced by recombinant DNA technology in an E. coli expression system. Therapeutically, anakinra neutralizes the biological activity of IL-1 (IL-1α and IL-1β) by competitively inhibiting its binding to the IL-1RI.

Kineret (anakinra) was first approved for treatment of RA in the US in 2001 and subsequently in the EU/EEA in 2002. More than 3000 patients were included in this development program.

In 2012, an sBLA on anakinra for treatment of NOMID was approved in the US. Kineret is also approved for treatment of CAPS (in EU/EEA, Israel and Australia), Still's disease, including SJIA and AOSD (in EU/EEA) and SJIA (in Australia).

The initial IND for anakinra was granted in 1991. The estimated cumulative exposure to anakinra in completed company sponsored clinical studies up to 1 May 2018 is 6404 subject-years in 8518 subjects with various indications.

Anakinra is administered s.c. at doses of 100 mg/day (RA) or in weight-based doses of up to 8 mg/kg/day (NOMID). In clinical studies in sepsis, doses up to 2 mg/kg/hour i.v. over 72 hours were administered to >500 patients and were well tolerated. For additional information of i.v. administration of anakinra, see Section 5.4.4.1.

Since the first approval in 2001 and up to 1 May 2018, it is calculated that the total post-marketing exposure of anakinra is >102 000 patient-years.

The safety profile of anakinra has been consistent across indications, age groups, and doses studied; this includes data that have been reported in the literature for off-label indications. The safety profile has remained stable also when anakinra has been studied in long-term safety studies and in patients with various co-morbidities. There are no indications of increasing AE rates over time. The most common AEs are non-serious, mostly mild to moderate injection site reaction that usually occur early and resolve during continued anakinra treatment. No dose-limiting toxicities have been observed in clinical studies or during post-marketing use and the maximum tolerated dose has not been established. There are no indications of changes to the safety profile even when very high doses are administered.

For the most recent information about anakinra, please refer to the current Summary of Product Characteristics (SPC).

Emapalumab (previously referred to as NI-0501, trade name Gamifant®) is a fully human Immunoglobulin G1 (IgG1) Anti-Interferon gamma (IFNγ) monoclonal antibody that binds to and neutralizes IFNγ.

Emapalumab binds to both soluble and receptor (IFNγR1)-bound forms of IFNγ.

Emapalumab is in development for the treatment of primary and secondary forms of HLH. The benefit expected from the targeted neutralization of IFNγ by emapalumab has been validated by the FDA approval in November 2018 of emapalumab for the treatment of patients with primary HLH who have refractory, recurrent or progressive disease or intolerance with conventional HLH therapy. The safety profile of emapalumab has been assessed as acceptable, and no post-marketing commitments have been requested by the FDA with regard to safety.

Since the start of the clinical development program for emapalumab, 103 patients have received emapalumab in clinical trials and through compassionate use. Furthermore, 70 patients have been treated to date in the US following FDA approval, and post-marketing surveillance has not revealed any additional safety concerns with the use of emapalumab.

Based on the analyses conducted to date, no sign of any off-target effect of emapalumab has been detected.

Multiple medications have been administered concomitantly with emapalumab and no evidence of significant drug-drug interactions has been reported so far.

For the most recent information about emapalumab, please refer to the current Investigator´s Brochure (version 10.0, dated 24, JAN, 2020).

The overall assessment is that the benefit of using anakinra and emapalumab as add-on to standard of care in patients diagnosed with SARS-CoV-2 infection outweighs the risks.

4 Study objectives and endpoints

4.1 Primary objective

The primary objective of this study is to assess the effect of emapalumab and anakinra on hyperinflammation and pulmonary function in patients with SARS-CoV-2 infection.

4.1.1 Primary endpoint

The primary endpoint is treatment success, defined as not requiring any of the following by Day 15:

- Invasive mechanical ventilation or
- Extracorporeal membrane oxygenation (ECMO).

4.1.2 Secondary endpoints supporting the primary objective

- Time to mechanical ventilation.
- Change from baseline in MEWs score.
- Change from baseline in resting SpO_2.
- Change from baseline in PaO_2/FiO_2.
- Change from baseline in hemogasanalysis.
- Change from baseline in oxygen supplementation.
- Amelioration of the findings of high-resolution CT scan of the chest.
- Change from baseline in hyperinflammatory parameters during treatment until Day 15 with measurements performed every 3 days:
    - Ferritin
    - LDH
    - D-dimers
- Change from baseline in other relevant laboratory parameters during treatment until Day 15 with measurements performed every 3 days:
    - WBC with differential counts
    - RBC
    - Hb

  - Platelet count
  - Fibrinogen
  - Complement C3/C4
  - Prothrombin time
  - Cardiac troponin
  - Liver tests (AST, ALT, total bilirubin levels)
  - CRP
  - Creatinine
- Overall survival.
- Time to hospital discharge.

4.2 Secondary objective

The secondary objective of this study is to evaluate the safety and tolerability profile of intravenous (i.v.) administrations of emapalumab and anakinra in patients with SARS-CoV-2 infection.

4.2.1 Secondary endpoints supporting the secondary objective

Safety endpoints of this study are:

- Treatment-emergent severe fatal and life-threatening serious adverse events (SAEs).
- Adverse events leading to premature discontinuation of study treatment.
- Anaphylactic/anaphylactoid reactions.
- Treatment emergent adverse events of special interest:
  - Emapalumab treatment group: Infections caused by pathogens potentially favored by IFN-γ neutralizations such as mycobacteria, salmonella, shigella, herpes zoster and histoplasma capsulatum, and severe infusion-related reactions.
  - Anakinra treatment group: Severe neutropenia.
- Treatment-emergent laboratory abnormalities.

4.3 Exploratory objective

An exploratory objective of this study is to assess the effect of anakinra and emapalumab on CXCL9, IL-1, IL-6, sIL-2R and selected biomarkers relevant for hyperinflammation, whenever possible.

4.3.1.1 Exploratory endpoints

Change from baseline in CXCL9, IL-1, IL-6, sIL-2R and selected biomarkers relevant for hyperinflammation.

5 Investigational plan

5.1 Overall study design and plan

This is a randomized, open-label, parallel group, 3-arm multicenter study to investigate the efficacy and safety of emapalumab and anakinra in reducing hyper-inflammation and respiratory distress in adult patients with a documented SARS-CoV-2 infection.

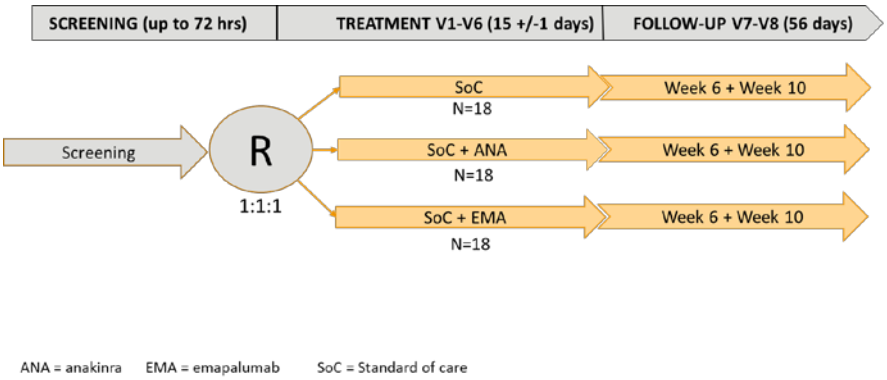
The study consists of screening, a 2-week treatment period and an 8-week follow-up period.

The 2-week treatment period is open, and the patients will be randomized to treatment with emapalumab, anakinra or standard of care in a 1:1:1 ratio. Emapalumab will be administered as i.v. infusions every 3rd day for a total of 5 infusions (Days 1, 4, 7, 10, 13). Anakinra will be administered as 4-times daily i.v. infustions for 15 days (Days 1 to 15). The primary endpoint will be evaluated at Day 15.

A follow-up by visit or phone call will be performed 4 and 8 weeks after the end of the treatment period (Weeks 6 and 10).

The study duration for an individual patient will not exceed 10 weeks. The end of the study is defined as last patient last follow-up visit/phone call.

Figure 1



The study design has a total sample size of 54 patients and consists of two stages. At the end of Stage 1, the success rates are compared between each of the two treatment arms and standard of care and there is the potential to stop for futility or for efficacy of emapalumab or anakinra.

A data review committee composed of experts in intensive care, inflammation, infection diseases will be involved in study oversight and interpretation of the study results.

In patients showing worsening of clinical condition, independently of the treatment arm, the Investigator is completely free to decide to introduce any drug considered necessary for a given patient as rescue treatment.

5.2 Discussion of study design, including the choice of control groups

5.3 Selection of study population

5.3.1 Inclusion criteria

A patient must fulfill the following criteria in order to be included in the study:

1. Signed informed consent provided by the patient, or by the patient's legally authorized representative(s), as applicable.
2. Documented presence of SARS-CoV-2 infection as per hospital routine.
3. Age > 30 to < 80 years at the time of screening.
4. Presence of respiratory distress, defined as:
    a. PaO_2/FiO_2 < 300 mm Hg and >200 mm Hg **or**
    b. RR ≥30 breaths/min **or**
    c. SpO_2 93% in air at rest.

    Note: Patients given CPAP ventilator support are eligible for inclusion.
5. Presence of hyperinflammation defined as:
    a. Lymphocyte counts < 1000 cells/mL, **and**
    b. Two of the following three criteria:
        i. Ferritin > 500ng/mL
        ii. LDH > 300 U/L
        iii. D-Dimers > 1000 ng/mL

5.3.2 Exclusion criteria

The presence of any of the following will exclude a patient from inclusion in the study:

1. Patients in mechanical ventilation or with MEWS score >4 with evidence of moderate or above ARDS (Berlin definition, namely with PaO_2/FiO_2 >100, but <200 mm Hg) or severe respiratory insufficiency or evidence of rapid worsening (respiratory distress requiring mechanical ventilation or presence of shock or presence of concomitant organ failure requiring ICU admission).
   Note: For the evaluation of patient eligibility, temperature will not be considered in the calculation of the total MEWS score since presence of fever is a hallmark of SARS-CoV-2 infection.
2. Impairment of cardiac function defined as poorly controlled heart diseases, such as NYHA class II (mild) and above, cardiac insufficiency, unstable angina pectoris, myocardial infarction within 1 year before enrollment, supraventricular or ventricular arrhythmia need treatment or intervention.

3. Severe renal dysfunction (estimated glomerular filtration rate ≤ 30mL/min/1.73 m^2) or receive continuous renal replacement therapy, hemodialysis, or peritoneal dialysis.
4. Uncontrolled hypertension (seated systolic blood pressure >180mmHg, or diastolic blood pressure >110mmHg) .
5. Administration of plasma from convalescent patients who recovered from SARS-CoV-2 infection.
6. Clinical suspicion of latent tuberculosis.
7. History of hypersensitivity or allergy to any component of the study drug.
8. Pregnant women.
9. Existence of any life-threatening co-morbidity or any other medical condition which, in the opinion of the investigator, makes the patient unsuitable for inclusion.
10. Enrollment in another concurrent clinical interventional study, or intake of an investigational drug within three months or 5 half-lives prior to inclusion in this study, if considered interfering with this study objectives as assessed by the Investigator.
11. Foreseeable inability to cooperate with given instructions or study procedures.

5.3.3 Withdrawal of patients from treatment or study

5.3.3.1 Withdrawal from treatment

A patient should be withdrawn from the study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient.

When a patient is withdrawn, the date of last IMP administration and the date and reason for treatment withdrawal should be clearly described in the relevant sections of the CRF. If a patient is removed from treatment because of an AE, the reason for treatment withdrawal should always be stated as ‘adverse event’ irrespective of whether this was the investigator’s or the patient’s decision.

The patient will continue to participate in the study without taking study treatment.

5.3.3.2 Withdrawal from study

Whenever possible and irrespective of the reason for withdrawal, the patient should be examined as soon as possible. Relevant samples should be obtained and all relevant assessments should be completed, preferably according to the schedule for Visit 6 (Day 15). The CRF should be completed as far as possible. Date and reason for the study withdrawal should be clearly described in the CRF.

5.3.4 Replacement of withdrawn patients

Patients withdrawn from the study will not be replaced.

5.3.5 Screening failures

Screening failures are defined as patients who consent to participate in the study but are not subsequently randomized into the study. A minimal set of screening failure information is required which includes demographics, reason for screen failure and failed eligibility criteria.

Patients who do not meet the criteria for participation in this study (screening failure) may not be rescreened.

5.4 Treatments

5.4.1 Treatments administered

The patients will receive investigational medicinal products (IMP) according to the randomization schedule, see Table 1.

Table 1 Investigational medicinal products

Arm	Investigational product	Dosage form	Route	Daily dose	Dosage regimen
A	Emapalumab	Solution	i.v. infusion	Day 1: 6 mg/kg Days 4, 7, 10, 13: 3 mg/kg	Every 3rd day for in total 5 infusions
B	Anakinra	Solution	i.v. infusion	Days 1-15: 400 mg/day in total, divided into 4 doses given every 6 hours	4 times daily for 15 days
C	None	N/A	N/A	N/A	N/A

5.4.2 Identity of investigational medicinal products

Emapalumab and anakinra will be supplied to the study sites as open-label supplies.

Possible deficiencies related to the handling and quality of the IMPs should be reported to the study monitor and also directly to complaints@sobi.com.

5.4.2.1 Emapalumab

The IMP emapalumab is delivered as a sterile concentrate for infusion, prefilled in single-use glass vials which require a dilution prior to administration. The concentrate of emapalumab in the solution is 5 mg/mL. The solution contains no antimicrobial preservative, and therefore each vial must be used only once.

Emapalumab should be stored between 2 and 8°C (36 and 46°F) in a secure area at the study sites. Further instructions on handling and storage of emapalumab are available in the IMP manual.

Emapalumab is manufactured by a third-party manufacturing facility duly qualified by Sobi AG and is supplied as described in the IMP Manual.

Labeling will comply with national regulatory requirements.

5.4.2.2 Anakinra

The IMP anakinra is delivered as a sterile solution for injection, prefilled in a single-use syringe with the strength 100 mg. The total volume of injection is 0.67 mL and the concentration of anakinra in the solution is 150 mg/mL.

Anakinra must be stored at refrigerated conditions at 2-8 °C (36°-46°F) in a secure area at the study sites. Further instructions for handling and storage of the IMP anakinra are available in the IMP manual.

The anakinra drug substance is manufactured by Boehringer Ingelheim (Vienna, Austria) or by Pfizer (Strängnäs, Sweden) and anakinra drug product is manufactured by Patheon Italia SpA (Monza, Italy).

Labeling will comply with national regulatory requirements.

5.4.3 Method of assigning patients to treatment groups

The different treatment groups are;

Arm A: Emapalumab as add on to standard of care
Arm B: Anakinra as add on to standard of care
Arm C: Standard of care only

The ratio between the treatment groups is 1:1:1, i.e., the same number of patients will be randomized to emapalumab, anakinra, or standard of care.

The randomization numbers are generated in blocks. Each block includes the three treatment groups per the ratio described above.

One randomization list will be prepared for each site with the first digit of the patient randomization number being specific for the site, and the second and third digits describing the consecutive number assigned at the site.

Sobi is responsible for generating the randomization schemes, which will link sequential patient randomization numbers to treatment codes.

5.4.4 Selection of doses

5.4.4.1 Dose selection rationale for anakinra

Anakinra is approved for the chronic treatment of a number of inflammatory diseases as a subcutaneous treatment (at doses of 100 mg/day or in weight-based doses of up to 8 mg/kg/day). The i.v. administration of anakinra has been studied in clinical trials in healthy volunteers and in critically ill patients with sepsis and hyper-inflammation at variable i.v. doses up to 3500 mg/day

over 72 hours: e.g., 2 mg/kg/hour, 20 mg/kg/day (<40 kg) and 916 mg/day (> 40kg), bolus of 100 mg followed by infusion of 2 mg/kg/hour. No safety concerns emerged in these studies [7, 8, 9, 10, and 11].

A study in children with systemic onset juvenile arthritis complicated by refractory macrophage activation syndrome is currently ongoing (NCT02780583) in which anakinra is administered at dose of 10 mg/kg/day to a maximum of dose of 200 mg/day divided every 12 hours (for children ≤40 kg) or 5 mg/kg/day up to a maximum dose of 400 mg/day divided every 6 hours (children > 40 kg and adults). This dosing schema reflects the dose at which anakinra is administered, although off label, in children affected by this severe disease, as reported in a number of case studies.

Based on the above, in this study anakinra is administered at a total dose of 400 mg per day, divided in 4 i.v. doses of 100 mg every 6 hours.

5.4.4.2 Dose selection rationale for emapalumab

Preliminary data on inflammatory makers in blood, e.g., D-dimer, LDH and ferritin [4, and unpublished data generated in the laboratory of Immunology of the National Institute for Infectious Diseases and the Laboratory of ImmunoRheumatology of the Ospedale Pediatrico Bambino Gesù] indicate that patients with SARS-CoV-2 infection have longer and more marked inflammatory response. This seems to be more evident in patients with severe disease. These markers, though elevated, appear to be less elevated than what is generally observed in systemic onset Juvenile Idiopathic Arthritis (sJIA) patients who develop Macrophage Activation Syndrome (MAS), a form of secondary HLH. Furthermore, their evolution over time seem to be also less rapid. Of note, it must be mentioned that these observations in blood may not fully reflect the amount of IFNγ released in the inflamed lungs.

The emapalumab dosing scheme used in the ongoing NI-0501-06 study in sJIA/MAS patients (NCT03311854) foresees an initial dose of 6 mg/kg followed by 3 mg/kg every 3 days. The available data in the 9 patients who have completed treatment to date indicate the achievement of complete response in all the patients with no relevant safety or tolerability concern [12]. In the trial in primary HLH, doses up to 10 mg/Kg/infusion have been used again with no relevant safety or tolerability concern [16].

Based on the above, an initial emapalumab dose of 6 mg/kg followed by 3 mg/kg every 3 days has been selected for the present study in SARS-CoV-2 infected patients.

This dose is considered appropriate to give the best chance to demonstrate efficacy in the specific patient population of this study, taking into account (I) the favourable safety profile of emapalumab not only in secondary, but also in primary HLH, (II) the life-threatening condition to be treated, (III) the low number of patients to be enrolled in the study (n=18), (IV) and the extremely challenging situation which the epidemic of SARS-CoV-2 infection represents.

5.4.4.3 Rationale for the use of glucocorticoids

Interim WHO guidance argues against the use of glucocorticoids in the treatment of patients with SARS-CoV-2 infection. “They should be avoided, because of the potential for prolonging viral

replication as observed in MERS-CoV patients, unless indicated for other reasons" (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html). However, evidence demonstrating a positive effect or a detrimental effect of glucocorticoids specifically in the treatment of patients with SARS-CoV-2 infection is lacking. In real life, glucocorticoids are being widely used in the treatment of patients in China (5 and13).

For SARS-CoV-2 infection, a growing body of evidence shows that hyper-inflammation appears to be particularly prominent in patients with severe disease, as well as in non-survivors compared to survivors [5 and 6]. All together these results points to high ferritin, high D-dimers and high LDH levels as being associated with poor outcome. Furthermore, initial data show the presence of hyperproduction of inflammatory cytokines with a profile similar to that present in patients with secondary hemophagocytic lymphohistiocytosis (sHLH) [5]. Unpublished data generated in the laboratory of Immunology of the National Institute for Infectious Diseases and the Laboratory of ImmunoRheumatology of the Ospedale Pediatrico Bambino Gesù confirm these findings with elevated levels of IL-1β, IL-6, TNF, and of the IFN-γ induced chemokines CXCL9 and CXCL10 being detected particularly in severe Covid-19 patients.

As glucocorticoids are one of the mainstay of first line anti-inflammatory treatment in sHLH, they have been suggested as one of the potential treatments for patients with severe SARS-CoV-2 infection [14]. Further to the relevance of the hyper-production of inflammatory cytokines in this infection, initial promising data have been reported with the use of IL-6 targeted therapies, namely tocilizumab, in the treatment of patients with SARS-CoV-2 infection [15]. Noteworthy, in this report all patients treated with tocilizumab received also glucocorticoids.

As this study is testing the hypothesis of the efficacy and safety of cytokine-targeted anti-inflammatory treatments in patients with SARS-CoV-2 infection and hyper-inflammation, it appears useful to evaluate these anti-inflammatory treatments with a background of glucocorticoids. Indeed, in sHLH, anakinra and emapalumab are both used with a background treatment of glucocorticoids [16, 12, and 17].

A short course of glucocorticoids, at low dose, is planned in order to minimize potential detrimental effect on virus clearance and avoid side effects related to long-term treatment with high-dose glucocorticoids.

5.4.5 Selection and timing of doses for each patient

5.4.5.1 Emapalumab

Emapalumab will be administered by intravenous (i.v.) infusion over a period of 1 to 2 hours depending on the volume to be infused, at an initial dose of 6 mg/kg.

Emapalumab treatment will be continued at the dose of 3 mg/kg, every 3rd day until Day 13 i.e., Days 4, 7, 10 and 13. The following information will be recorded in the CRF for each emapalumab administration: date, start and end time, total dose infused, and, if infusion was interrupted, reason for interruption.

Emapalumab must be prepared by a Pharmacist or other appropriately qualified staff member, specifically authorized by the Investigator/Pharmacist and appropriately licensed to perform the task.

The specific dose to be administered for an individual infusion will be determined based on the patient´s body weight at screening.

Full instructions for the preparation of emapalumab, including dilution steps and method for administration, are available in the IMP manual.

The patient should receive the designated volume of the infusion material through an infusion pump over 1 to 2 hours depending on the volume to infuse. A 0.2 μm filter must be included in all infusion lines.

It is recommended that an i.v. central line remains in place to ensure venous access during the treatment period.

Since no data are available on the compatibility of emapalumab with other i.v. substances or additives, other medications/substances should not be added to the infusion material or infused simultaneously through the same i.v. line. If the same i.v. line is used for subsequent infusions of other drugs, the line should be flushed appropriately with saline before and after infusion of emapalumab.

5.4.5.2 Anakinra

Anakinra will be administered by i.v. infusion at total dose of 400 mg per day, divided in 4 doses 100 mg i.v. every 6 hours.

Anakinra treatment will continue for 15 days i.e., Days 1 to 15. The following information will be recorded in the CRF for each anakinra administration: date, start and end time, total dose infused, and, if infusion was interrupted, reason for interruption.

Before administration, the full content of the prefilled, single-use syringe (anakinra 100 mg) will be diluted in 100 mL saline. The i.v. administration of anakinra has to occur immediately after the preparation over an infusion period of 60 minutes.

Full instructions for the preparation of anakinra are available in the IMP manual.

5.4.6 Blinding and unblinding

This is an open study with no level of blinding.

5.4.7 Concomitant therapy

5.4.7.1 Background therapy

All patients participating in the study will receive background therapy with methylprednisolone. In case a patient is not already receiving methylprednisolone, treatment will be initated at the time of the first study drug administration (Visit 1, Day 1). In case the patient is already

receiving glucocorticoids, independently of the type of glucocorticoids and the dose previously administered, the patient will receive methylprednisolone at the dose of 20 mg 3 times per day from Day 1.

As methylprednisolone is background therapy and not a study drug, it will not be provided by Sobi.

Background therapy will be administered according to the dosing schedule in Table 2.

Table 2 Dosing schedule of methylprednisolone

Study Day	Dose and dosage regimen
Days 1-5	20 mg of methylprednisolone 3 times per day i.e., 60 mg/day
Days 6-10	10 mg of methylprednisolone 3 times per day i.e., 30 mg/day
Days 11-14	5 mg of methylprednisolone 3 times per day i.e., 15 mg/day

The background therapy will be recorded in the CRF.

5.4.7.2 Concomitant therapy

Concomitant use of IL-6 inhibitors (e.g., tocilizumab), non-anakinra IL-1 inhibitors (e.g, canakinumab), TNF inhibitors, JAK inhibitors and hydroxychloroquine is **not** allowed. If any of these therapies are initiated at the discretion of the Investigator e.g., as rescue therapy due to worsening of the patient's condition, then the patient should be withdrawn from study (see Section 5.3.3.2).

Antimicrobial therapy and prophylaxis are not limited.

Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, i.v. parenteral nutrition, inotropic support, antibiotics, anti-fungal and anti-viral treatments, ultrafiltration or hemodialysis, as well as general supportive care are permitted.

Other therapy considered necessary for the patient's welfare may be given at the discretion of the Investigator.

All relevant concomitant therapy, as defined by the Investigator, will be recorded in the CRF.

5.4.8 Treatment compliance

The IMP administrations will be recorded in the CRF as described in Section 5.4.5.

Product accountability records will be kept. The pharmacy and Investigator must maintain accurate records demonstrating date and amount of study drug(s) received, to whom and by whom administered or dispensed (patient-by-patient accounting), and accounts of returned study drug (s) and any study drug accidentally or deliberately destroyed. All unused study drug will be counted.

At the end of the study, any remaining study drug (s) will be destroyed locally or returned to the depot for destruction. In either case, a certificate of destruction must be issued.

5.5 Efficacy and safety assessments

5.5.1 Study schedule

5.5.1.1 Schedule of events

Table 3 Schedule of Events

ASSESSMENT	SCREENING	TREATMENT PERIOD						FOLLOW-UP PERIOD	
	Up to 72h prior to Visit 1	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7/TC	Visit 8/TC
		Day 1 (Baseline)	Day 4	Day 7	Day 10	Day 13	Day 15 (± 1 day)	Week 6 (± 5 days)	Week 10 (± 5 days)
Informed consent	X								
Eligibility criteria	X	X[1]							
Patient information[2]	X								
Physical examination[3]	X								
Vital signs assessment[4]	X	X	X	X	X	X	X		
ECG assessment	X						X		
HRCT scan of chest	X[5]						X		
Laboratory assessments (local)[6]	X[5]	X	X	X	X	X	X		
Urine pregnancy test[7]	X						X		
Randomization		X							
IMP administration[8]		X----------					----------X		
Concomitant medication incl background therapy[9]		X	X	X	X	X	X		
Pulmonary function[10]		X	X	X	X	X	X		
PaO_2/FiO_2	X						X		
Resting SpO_2 (3 times per day)		X	X	X	X	X	X		
Hemogasanalysis		X	X	X	X	X	X		
Oxygen supplementation		X	X	X	X	X	X		
MEWS score		X					X		
Survival								X	X
Time to hospital discharge								X	X
Adverse events[11]		X	X	X	X	X	X		
Biomarkers[12]		X	X	X	X	X	X		

Abbreviations: CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; HRCT, high resolution computed tomography; IMP, Investigational Medicinal Product; MEWS, modified early warning system; PaO_2, partial pressure of oxygen; SpO_2, peripheral capillary oxygen saturation
During the treatment period (Days 1 to 15), clinical and laboratory assessments and procedures should preferably be performed before IMP administration.
[1]Before study drug administration.
[2]Includes demographics, medical and surgical history and prior medication.
[3]Including recording of body weight and length.
[4]Body temperature, blood pressure, heart rate, respiratory rate and oxygen saturation.
[5]HRCT scan results and laboratory results already available in medical records at the time of informed consent can be used to confirm eligibility, if collected within 72 hours.
[6]Ferritin, LDH, D-dimers. WBC with differential counts, RBC, Hb, Platelet count, Fibrinogen, Complement C3/C4, Prothrombin Time, Cardiac troponin, AST, ALT, total bilirubin levels, CRP and Creatinine.
[7]Only applicable for females of childbearing potential.
[8]Emapalumab will be administered once daily Days 1, 4, 7, 10 and 13 (Section 5.4.5.1). Anakinra will be administered 4 times daily for 15 days i.e., Day 1 to 15 (Section 5.4.5.2).
[9]For details, see Section 5.4.7.
[10]Requirement for invasive mechanical ventilation or ECMO.
[11]Incidence, severity, causality and outcomes of treatment-emergent severe fatal and life-threatening serious AEs, including anaphylactic and anaphylactoid reactions to study drugs, adverse events leading to premature discontinuation of study treatment and adverse events of special interest.
[12]CXCL9, IL-1, IL-6, sIL-2R. To be assessed whenever possible.

5.5.1.2 Screening

Screening will occur up to 72 hours prior to Visit 1 (Baseline). The aim of the screening is to collect necessary data to confirm the patient's eligibility and can be ongoing up the randomization of the patient at Visit 1. A signed informed consent form must be obtained from the patient prior to any study-related activities. However, HRCT scan results and laboratory results already available in medical records at the time of informed consent can be used to confirm eligibility, if collected within 72 hours. Please refer to Table 3 for the clinical and laboratory parameters to be collected during screening.

Patients who do not meet the criteria for participation in this study (screening failure) may not be rescreened.

5.5.1.3 Visit 1, Baseline (Day 1)

Once all inclusion and exclusion criteria have been reviewed and recorded, and the patient has been found eligible, the patient will be randomized into one of the treatment groups and the first dose of study drug will be administered accordingly (see Section 5.4.5). Please refer to Table 3 for other clinical and laboratory parameters to be collected during the visit.

During the treatment period (Days 1 to 15), clinical and laboratory assessments and procedures should preferably be performed before IMP administration.

5.5.1.4 Visits 2 to 5 (Days 4, 7, 10 and 13)

Please refer to Table 3 for the clinical and laboratory parameters to be collected during these visits. For study drug administration schedule, see Section 5.4.5.

Effort should be made to adhere to the schedule of assessment. However, a window of ±1 day will be allowed for all assessments scheduled for Visits 2 to 5. This does not include IMP administration.

During the treatment period (Days 1 to 15), clinical and laboratory assessments and procedures should preferably be performed before IMP administration.

5.5.1.5 Visit 6 (Day 15)

Please refer to Table 3 for the clinical and laboratory parameters to be collected during these visits. For study drug administration schedule, see Section5.4.5.

Effort should be made to adhere to the schedule of assessment. However, a visit window of ±1 day will be allowed for Visit 6 (Day 15).

During the treatment period (Days 1 to 15), clinical and laboratory assessments and procedures should preferably be performed before IMP administration.

The primary endpoint will be evaluated at Visit 6 (Day 15).

5.5.1.6 Visits 7 and 8, Follow-up (Weeks 6 and 10)

These visits can be conducted either as a follow-up telephone call or in-person visit, if the patients is still hospitalized. Please refer to Table 3 for the clinical parameters to be collected during the visits.

A window of ±5 days will be allowed for Visits 7 and 8.

5.5.2 Patient information and physical examination

5.5.2.1 Demographics

The patient´s date of birth, gender, race and ethnicity will be collected at screening, and recorded in the CRF.

5.5.2.2 Medical and surgical history

Details of the patient's relevant medical and surgical history as judged by the Investigator will be collected at screening, and recorded in the CRF.

5.5.2.3 Prior medication

Details of the patient's relevant prior medication as judged by the Investigator will be collected at screening, and recorded in the CRF.

5.5.2.4 Physical examination

A general physical examination will be performed at screening and recorded in the CRF. The assessment will be reported as "normal" or "abnormal". Any abnormalities should be specified and recorded as medical history.

Body weight and height will be recorded as a part of the physical examination.

5.5.3 Efficacy assessments

5.5.3.1 Pulmonary function (primary efficacy assessment)

The date and time of the requirement for invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO) will be assessed at Visits 1 to 6, and recorded in the CRF.

5.5.3.2 MEWS score

Modified early warning system score (MEWS) will be assessed at Visit 1 (Day 1) and Visit 6 (Day 15), and recorded in the CRF.

5.5.3.3 SpO_2, PaO_2 and FiO_2

Resting peripheral capillary oxygen saturation (SpO_2) will be measured 3 times per day at Visits 1 to 6, and recorded in the CRF.

The partial pressure of oxygen (PaO_2) and the fraction of inspired oxygen (FiO_2) will be measured at screening and at Visit 6, and recorded in the CRF.

5.5.3.4 Hemogasanalysis

Hemogasanalysis will be assessed at Visits 1 to 6, and recorded in the CRF.

Analysis may for example include pH, carbon dioxide tension (pCO_2), oxygen tension (pO_2), electrolytes, lactate and hemoglobin.

5.5.3.5 Oxygen supplementation

Oxygen supplementation will be assessed at Visits 1 to 6. The date, time and amount of supplementation will be recorded in the CRF.

5.5.3.6 High-resolution computed tomography

A high-resolution computed tomography scan (HS-CT) of the chest will be performed at screening and Visit 6 (Day 15). The HS-CT scan will be recorded in the CRF and reported as "normal" or "abnormal".

Any abnormalities reported at screening should be specified and recorded as medical history.

5.5.3.7 Laboraratory assessments

Blood samples for determination of the laboratory assessments described in Table 4 will be drawn at screening, and at Visits 1 to 6. The date and time of blood sampling will be recorded in the CRF.

Table 4 Laboratory assessments

Biochemistry	**Hematology**
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin (if >upper limit of normal also conjugated and non-conjugated bilirubin) Prothrombin Time/International Normalized Ratio (PT-INR) Fibrinogen Complement C3/C4 Cardiac troponin Creatinine C-reactive protein (CRP)	Hemoglobin Platelet count White blood cells RBC Differential blood count **Hyperinflammatory parameters** Ferritin LDH D-dimers

All laboratory samples will be analysed at the respective local hospital laboratory according to their standard routines.

The laboratory results will be sent by the respective hospital to Sobi via regular mail, or scanned and sent via email after proper masking/redacting of patient ididentification information (e.g. patient name, patient ID, patient initials, patient address) and any test results which are not to be collected as part of this study.

5.5.3.8 Survival and hospital discharge

Data on survival and hospital discharge will be collected at Visits 7 and 8 (Weeks 6 and 10) and recorded in the CRF.

5.5.4 Safety assessments

5.5.4.1 Adverse events

5.5.4.1.1 Definitions

Adverse event (AE)

An AE is any adverse change, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a patient during the course of the study, whether or not considered by the investigator as related to study treatment.

A treatment-emergent AE is any AE temporally associated with the use of study treatment whether or not considered by the investigator as related to study treatment.

Adverse events include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of the study even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen following the start of the study (i.e., signing of informed consent).
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities are considered as AEs if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.An AE is any untoward medical occurrence in a patient administered a pharmaceutical product; the event does not necessarily have a causal relationship with the treatment or usage.

5.5.4.1.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE pages of the CRF.

If the intensity of an AE worsens during study treatment administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

If the intensity of an AE with an onset date between informed consent signature and start of study treatment and which is ongoing at the start of treatment worsens after the start of study treatment, a new AE page must be completed. The onset date of this new AE corresponds to the date of worsening in intensity.

The three categories of intensity are defined as follows:

- Mild

The event may be noticeable to the patient. It does not influence daily activities, and usually does not require intervention.

- Moderate

The event may make the patient uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- Severe

The event may cause noticeable discomfort, and usually interferes with daily activities. The patient may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious, see Section 5.5.4.2. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than severity assessment, determines the regulatory reporting obligations.

5.5.4.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated. The determination of the likelihood that the study treatment caused the AE will be provided by an investigator who is a qualified physician.

5.5.4.2 Serious adverse events

5.5.4.2.1 Definitions of serious adverse events

An SAE is defined by the International Conference on Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring inpatient hospitalization, or prolongation of existing hospitalization.

- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the patient, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are exempted from being reported:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.

However, complications that occur during hospitalization are AEs or SAEs (for example if a complication prolongs hospitalization).

5.5.4.3 Reporting requirement of adverse events

5.5.4.3.1 Reporting of adverse events

Irrespective of seriousness, the following adverse events are considered as adverse events of special interest and must be reported on AE page of the CRF.

In all patients:

- AEs leading to discontinuation study treatment
- Anaphylactic/anaphylactoid reactions

In patients treated with emapalumab, the following AEs will be considered of special interest:

- infections caused by pathogens potentially favored by IFN-γ neutralizations such as mycobacteria, salmonella, shigella, herpes zoster, and histoplasma capsulatum.
- severe infusion related reactions defined as any severe AE occurring within 24 hours of infusion initiation and assessed as causally related by the investigator.

In patients treated with anakinra, the following AEs will be considered of special interest:

- severe neutropenia defined as neutrophil count < 500/mm^3.

No other AEs are required to be reported on the AE page of the CRF

5.5.4.3.2 Reporting of serious adverse events

All fatal and life-threatening SAEs occurring after study drug initiation and up to the end of study visit (Visit 8, Week 10) must be reported on AE pages in the CRF and on an SAE form, regardless of the investigator-attributed causal relationship with study treatment.

No other SAEs are required to be reported on AE page of the CRF and on the SAE form to the Sponsor.

Abnormal laboratory findings

Abnormal laboratory findings, if serious (fatal or life-threatening), must be reported on specific AE pages of the CRF.

Following laboratory variables are collected for the assessment of efficacy (see Section 6.5.3.2) at screening and during the treatment period, and are not required to be reported as SAEs as described above: WBC including differential counts, RBC, Hgb, platelet count, fibrinogen, complement C3/C4, PT-INR, and cardiac troponin; ALT, AST, total bilirubin, creatinine, ferritin, LDH, D-dimer, and CRP.

5.5.4.3.3 Follow-up of serious adverse events

Serious adverse events still ongoing at the end of study visit (Visit 8, Week 10) must be followed up until resolution or stabilization, or until the event outcome is provided, e.g., death.

5.5.4.3.4 Reporting procedures

All fatal and life-threatening SAEs must be reported by the investigator to the Sobi drug safety department within 24 hours of the investigator's first knowledge of the event.

All fatal and life-threating SAEs must be recorded on an SAE form, irrespective of the study treatment received by the patient, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be e-mailed to the Sobi drug safety department:

- NI-0501drugsafety@sobi.com

The investigator must complete the SAE form in English, and must assess the causal relationship of the event to study treatment.

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Sobi drug safety department may contact the investigator to obtain further information.

If the patient is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation.

The reference safety document to assess expectedness of a suspected serious adverse reaction and for reporting by the Sponsor to Health Authorities, IRBs/IECs, and investigators is:

- For emapalumab - the reference safety information section of the Investigator's Brochure [Emapalumab IB].
- For anakinra - Section 4.8. of anakinra SmPC (Kineret SmPC) + i.v. data

5.5.4.4 Pregnany

5.5.4.4.1 Reporting of pregnancy

Irrespective of the treatment received by the patient, any pregnancy occurring after study drug initiation up to the end of study visit (Visit 8, Week 10) must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the pregnancy form which is e-mailed to the Sobi drug safety department (NI-0501drugsafety@sobi.com), and on an AE page in the CRF.

5.5.4.4.2 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion and its outcome must be reported to the Sobi drug safety department. This information will be only entered in the drug safety database.

Any AE associated with the pregnancy occurring during the study must be reported on separate AE pages in the CRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 5.5.4.3.

5.5.4.5 Study safety monitoring

Clinical study safety information is monitored and reviewed on a continuous basis by the Sobi Clinical Team (in charge of ensuring patients' safety as well as data quality) by periodically monitoring clinical studies activities from protocol conception to database closure.

5.5.4.6 Laboratory safety assessments

For details on laboratory assessments, see Section 5.5.3.7.

5.5.4.7 Vital signs

Vital signs (body temperature, blood pressure, heart rate. respiratory rate and oxygen saturation) will be measured at screening, and Visit 1 to 6, and recorded in the CRF.

For AE reporting of abnormalities, see Section 5.5.4.3.

5.5.4.8 Electrocardiograms

A 12-lead ECG recording will be performed at screening and at Visit 6 (Day 15), and recorded in the CRF. The ECG assessments will be peformed at site and will be reported as "normal" or "abnormal". Any abnormalities should be specified. Abnormalities reported at screening should be recorded as medical history.

For AE reporting of abnormalities, see Section 5.5.4.3.

5.5.4.9 Pregnancy Test

Female of childbearing potential will have a urine pregnancy test taken at screening and at Visit 6 (Day 15). The outcome of the test will be reported as "positive" or "negative" in the CRF.

5.5.4.10 Data Review Committee

The Data Review Committee composed of experts in intensive care, inflammation, infectious diseases will be involved in study oversight and interpretation of the study results.

5.5.4.11 Safety Review Committee

Clinical safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and study-specific labs/examinations, as required) will be monitored and reviewed on a continuous basis by the Safety Review Committee (SRC) by periodically monitoring clinical studies activities from protocol conception to database closure. There will be separate written operating procedures for the SRC.

5.5.5 Exploratory assessments

Blood samples for determination of CXCL9, IL-1, IL-6, sIL-2R and selected exploratory parameters will be collected at Visit 1 to 6, whenever possible. The date and time of sampling will be recorded in the CRF.

All samples will be analyzed at the respective hospital local laboratory according to their standard routines.

The laboratory results will be sent by the respective hospital to Sobi via regular mail, or scanned and sent via email after proper masking/redacting of patient ididentification information (e.g. patient name, patient ID, patient initials, patient address) and any test results which are not to be collected as part of this study.

6 Quality control and quality assurance

This study will be conducted in compliance with this protocol, study specific procedures, Sobi SOPs, the ICH Guideline for GCP [1], and applicable regulatory requirements.

The Sponsor will establish a systematic, prioritized, risk-based approach to monitoring and, considering the current situation, will need to utilize remote monitoring. The Sponsor will develop a risk management plan with the aim to limit the contacts with patients and site personnel during the emergency period, while ensuring the patients safety and integrity, compliance with the protocol, study specific procedures and applicable regulatory requirements.

To ensure ongoing patient safety and well-being, and control risks to study critical processes, such as review of all informed consent forms and all primary efficacy variables, alternative mechanisms of oversight will be introduced (such as phone calls, video calls etc). The Sponsor will also investigate if other measures for sharing data can be implemented, e.g. sharing de-identified source documents in shared drives/locations.

On-site monitoring visits will be postponed until the emergency period is over. Source documents will then be reviewed for verification of agreement with data in CRFs.

The investigator or institution guarantees access to source documents by Sobi, its representatives, and appropriate regulatory agencies.

The study site may be subject to a quality assurance audit by Sobi or its representatives, as well as inspection by appropriate regulatory agencies.

It is important that the investigator(s) and the(ir) relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

7 Statistical plan

7.1 Determination of sample size

The study will enroll a total of 54 patients, 18 per arm according to the 1:1:1 randomization.

The sample size has been estimated based on the following assumptions:

- An overall one-sided significance level for efficacy of 0.097 (9.7%) and a power of 74% for each comparison under the assumption that the true success rates are 50% in the SoC group increasing to 80% in the emapalumab or anakinra groups.
- The study will consist of two stages, with equal numbers of patients randomised into Stage 1 and into Stage 2 per treatment arm.
- There is the potential to stop for futility or for efficacy of emapalumab or anakinra (or both) at the end of Stage 1.
- The futility rule for stopping at the end of Stage 1 is binding.

More specifically:

- The emapalumab or anakinra arm (or both) will be stopped at the end of Stage 1 for futility if the one-sided p-value in favour of emapalumab/anakinra is > 0.690.
- The emapalumab or anakinra arm (or both) will be stopped for efficacy at the end of Stage 1 if the one-sided p-value in favour of emapalumab/anakinra is < 0.025.
- If the trial continues to Stage 2, efficacy will be declared at the end of Stage 2 if the one-sided p-value in favour of emapalumab/anakinra is < 0.159.

The calculations on the operating characteristics of this design have been undertaken using PASS, Version 14: Group-Sequential Tests for Two Proportions (Simulation).

The value for the type I error has been chosen in recognition of the urgent unmet medical need to allow the identification of a signal, at least, from a statistical perspective. Having seen a statistical signal, it is then a matter of evaluating whether the observed treatment differences represent clinically relevant effects that can satisfy that unmet need.

In case indications of efficacy requires to be confirmed, additional patients may be added into this study.

In case the outcome is statistically convincing, efficacy will be considered confirmed and the results will, where warranted, be used to seek regulatory approvals.

7.2 Definition of study populations

All efficacy and safety analyses will be conducted on the All Treated population which will comprise all randomized patients receiving study treatment.

Patients will be included in the groups to which they were randomized for all evaluations of efficacy and in the groups according to treatment received for all evaluations of safety.

7.3 Overall statistical and analytical plan

Statistical analysis will be performed using SAS software Version 9.4 or later (SAS Institute, Inc, Cary, North Carolina, United States).

7.3.1 General statistical issues

This design has acceptable properties in terms of the false positive potential, controlling the overall type I error at 9.7%, for each of the two treatment comparisons.

Secondary endpoints will be evaluated in a descriptive way. In some cases p-value comparisons will be undertaken, but these are to be interpreted in an exploratory way.

7.3.2 Demographics and baseline characteristics

Demographic and baseline characteristics will be summarized in appropriate tabular presentations.

For measurements of continuous endpoints, summary statistics will include n, mean, median, standard deviation, minimum and maximum values. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented.

7.3.3 Analysis related to primary objective

7.3.3.1 Primary endpoint

7.3.3.1.1 Treatment success

For the analysis of the primary endpoint, each of the pairwise comparisons, emapalumab/anakinra versus standard of care, at both the end of Stage 1 and at the end of Stage 2, will be undertaken using Fishers Exact test comparing the proportion of patients with treatment success. The p-value calculations will be supplemented by the presentation of one-sided exact confidence intervals, with confidence coefficients of 97.5% at the end of Stage 1 and 84% at the end of Stage 2, using the method of Clopper-Pearson [18].

7.3.3.2 Secondary endpoints supporting the primary objective

7.3.3.2.1 Time to mechanical ventilation and overall survival

Analysis of the time to mechanical ventilation from the point of randomization will be undertaken by plotting Kaplan-Meier curves for each of the 3 treatment groups and by pairwise comparisons (emapalumab/anakinra versus standard of care) using the logrank test. Hazard ratios will be estimated using the Cox proportional hazards model and these will be presented together with 90% two-sided confidence intervals.

Overall survival (time to death from the point of randomization) and time to hospital discharge (from the point of randomization) will not be analysed at the end of Stage 2, but at the end of the follow-up period. This endpoint will be analysed as for time to mechanical ventilation.

7.3.3.2.2 Change from baseline in MEWs score

Change from baseline in MEWs score at Day 15 will be analysed using analysis of covariance (ANCOVA) including treatment arm as a fixed factor and baseline MEWs score as a covariate. Least square mean change per group, associated 90% two-sided CI, and p-values for the comparison vs. standard of care, will be presented.

7.3.3.2.3 Change from baseline in hyperinflammatory parameters

Change from baseline during treatment until Day 15 with measurements performed every 3 days of the following parameters will be summarized using descriptive statistics:

- Ferritin
- LDH
- D-dimers

7.3.3.2.4 Change from baseline in other relevant laboratory parameters

Change from baseline during treatment until Day 15 with measurements performed every 3 days of the following parameters will be summarized using descriptive statistics:

- WBC with differential counts
- RBC
- Hb
- Platelet count
- Fibrinogen
- Complement C3/C4
- Prothrombin Time
- Cardiac troponin
- Liver tests (AST, ALT, total bilirubin levels)
- CRP
- Creatinine

7.3.3.2.5 Change from baseline in resting SpO_2 and oxygen supplementation

Change from baseline during treatment until Day 15 with measurements performed every 3 days will be summarized using descriptive statistics for each of these parameters.

7.3.3.2.6 Change from baseline in PaO_2/FiO_2

Change from baseline (screening) during treatment until Day 15 will be summarized using descriptive statistics.

7.3.3.2.7 Change from baseline in hemogasanalysis

Change from baseline during treatment until Day 15 with measurements performed every 3 days will be summarized using descriptive statistics for each of the collected parameters.

7.3.4 Analysis related to secondary objective

7.3.4.1 Adverse events

Reported AEs during the study will be coded using MedDRA. The incidence of AEs will be summarized in frequency tables by treatment, system organ class, preferred term and maximum severity. Separate tabulations will performed for serious and non-serious AEs.

7.3.5 Interim analysis

The study will consist of one interim analysis (Stage 1) and a final analysis (Stage 2), with approximately the same numbers of patients randomised into Stage 1 and into Stage 2 per treatment arm. The Stage 1 interim analysis will be conducted after the accrual of at least 9 patients per treatment arm. See Section 8.1 for further details concerning the interim analysis.

7.3.6 Multiple comparison/multiplicity

There will be no adjustments for multiplicity for the two pairwise treatment comparisons for the primary endpoint. Multiplicity for the sequential comparisons at the end of Stage 1 and at the end of Stage 2 are however accounted for by the design.

7.3.7 Handling of missing data

There will be no imputation of missing data.

8 Data collection, handling and record keeping

8.1 Data standards

Collection of data should be performed in the CDASH format, according to the CDISC. The standards should be used to the extent possible and/or required for the specific study/project. The minimum requirement of the CDISC standard is to collect all core variables specified as 'Required' in the Study Data Tabulation Model format.

8.2 Case report form

A CRF is required and should be completed for each included patient. In this study, a paper CRF will be used to capture all study data except for the scheduled laboratory results from the hospital´s local laboratory. The completed original CRFs are the sole property of Sobi and should not be made available in any form to third parties without written permission from Sobi, except for authorized representatives of appropriate Regulatory Authorities.

It is the responsibility of the Principal Investigator to ensure the completeness, legibility, and accuracy of the data reported in the CRF, to review and to confirm these by proving his/her signature, thus approving all CRFs pages. The Principal Investigator must sign off each visit in the CRF using black ballpoint pen, in addition to providing a final signature of the completed CRF. These signatures serve to attest that the information contained on these CRFs is correct. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

The CRF pages should either be copied and sent to Sobi via regular mail, or scanned and sent via email. In either case, it is important that the original CRF pages remain at site.

The laboratory results from local laboratories will be sent by the respective hospital to Sobi via regular mail, or scanned and sent via email after proper masking/redacting of patient ididentification information (e.g. patient name, patient ID, patient initials, patient address) and any test results which are not to be collected as part of this study.

Sobi will enter all collected data in a clinical database as per internal routines following a double-data-entry process.

8.3 Source data

Patient source documents are the patient's medical records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart, including laboratory test results, radiology results, ECG etc. In those cases, the information collected in the CRFs must match those charts.

A separate source document location agreement will be completed and signed by the Principal Investigator and the site monitor.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trial).

8.4 Protocol deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of patients. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study patients.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

When a deviation from the protocol is identified, the investigator or designee must ensure Sobi is notified. Sobi will follow up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and / or efficacy of the patient to determine patient continuation in the study.

The investigator must contact Sobi immediately if a deviation is discovered that significantly affects or has the potential to significantly affect human subject protection or the reliability of study results.

The investigator will also assure that deviations are reported and documented in accordance with IEC and applicable regulatory requirements.

8.5 Database closure

Prior to database closure, all tasks or criteria defined in the data management plan must be completed and documented. The study database must be locked before generation of any results. The database lock will be approved by relevant study personnel and all edit accesses will be removed. Following database closure, the study database can only be unlocked in case critical errors, affecting the main conclusions of the study, are discovered.

8.6 Record retention

The investigator should maintain a record of the location(s) of investigator’s essential documents as defined in the ICH GCP Guideline [1] including source documents and should have control of and continuous access to all essential documents and records generated by the investigator/institution before, during, and after the study.

All documents and data relating to the study will be kept securely by the investigator in a secure file and/or electronically. The storage system used during the study and for archiving (irrespective of the type of media used) should provide for document identification, version

history, search and retrieval. The data will be available for evaluation and/or audits from Health Authorities, Sobi or Sobi's representatives.

When a copy is used to replace an original document (e.g. source documents, CRF), the copy should fulfill the requirements for certified copy as defined in ICH GCP Guideline [1].

The records should be retained by the Investigator as specified in the Clinical Trial Agreement and in accordance with local regulations.

If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator or another institution. Archiving on behalf of the investigator can also be delegated to Sobi.

9 End of study

The end of this study is defined as the date of the last patient's last visit/end of study call (Visit 8, Week 10).

10 Sponsor's discontinuation criteria

Sobi reserves the right to discontinue the study prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating patients within 30 days. All study materials must be collected and all the CRFs completed to the greatest extent possible.

11 Dissemination and publication of results

Sobi will register the study by posting study information and post study results regardless of outcome on a publicly accessible website in accordance with applicable laws and regulations, e.g., on www.clinicaltrials.gov and EudraCT. The results of this study will be published within 12 months of the end of study.

Sobi is committed to publishing study results in a complete, accurate, balanced, transparent and timely manner. Sobi follows the principles of the International Committee of Medical Journal Editors (ICMJE) recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals including criteria for authorship [3].

The data from this study will be considered for reporting at a scientific meeting or for publication in a scientific journal. The Sponsor will be responsible for these activities and will work with the investigators to determine how the publication is written, the number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues. The results of the study, or any part thereof, shall not be published without the prior written consent and approval of Sobi, such consent and approval not to be unreasonably withheld.

12 Reference list

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3 International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals: updated December 2016 [Internet]. International Committee of Medical Journal Editors (ICMJE); 2016. [cited 2017 Jan 12]. Available from: http://www.icmje.org/recommendations/

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18 Clopper C et al. The use of confidence or fiducial limits illustrated in the case of the Binomial. Biometrika 1934;26: 404-413

Appendix 1 Additional Protocol Signatures

Sponsor's Clinical Program Leader

Karin Becker, MSc Pharm
Clinical Program Leader
E-mail: karin.becker@sobi.com

DocuSigned by:
Karin Becker
Signer Name: Karin Becker
Signing Reason: Jag godkänner dokumentet
Signing Time: 20 March 2020 | 21:03:28 CET
C55B3EC6C36A49F3BC526D2C1141F604

Signature

20 March 2020 | 21:03:32 CET

Date

Sponsor's Statistician

Henrik Andersson, MSc
Statistician
E-mail: henrik.andersson@sobi.com

DocuSigned by:
Henrik Andersson
Signer Name: Henrik Andersson
Signing Reason: Jag godkänner dokumentet
Signing Time: 20 March 2020 | 13:13:29 PDT
40F3D60C048844FEB4B1AFE3D0BEEF64

Signature

20 March 2020 | 13:13:33 PDT

Date

Appendix 2 Study Administrative Structure

Sponsor:	Swedish Orphan Biovitrum AB (publ), SE-112 76 Stockholm, Sweden Phone: +46 8 697 20 00
Study sites:	3 to 5 study sites in Italy.
Monitoring:	Swedish Orphan Biovitrum AB (publ).
SAE reporting:	Swedish Orphan Biovitrum AB (publ).
Data management:	Swedish Orphan Biovitrum AB (publ).
Statistics:	Swedish Orphan Biovitrum AB (publ).
Investigational products (production):	See Section 5.4.2.
Investigational products (packaging and labeling):	Rechon Life Science AB (Limhamn, Sweden).
Clinical laboratory:	All clinical laboratory assessments, including assessments of biomarkers, will be performed at the local hospital.

Appendix 3 Exemption Letter

AIFA
Italian Medicines Agency
Via del Tritone, 181
I-00187 Roma
Italy

March 16, 2020

Dear Sirs,

Re: Clinical trial of emapalumab and anakinra in patients with Coronavirus disease (COVID-19)

Swedish Orphan Biovitrum AB is planning to conduct a clinical trial with emapalumab and Kineret (anakinra) in patients with Coronavirus disease (COVID-19) and hyperinflammation.

The protocol (Sobi.IMMUNO-101, EudraCT **2020-001167-93**) has been prepared in response to the request from the President of the Italian Consiglio Superiore di Sanità, Prof. Franco Locatelli, and the Scientific Director of the National Institute for Infectious Diseases (Ospedale Lazzaro Spallanzani, coordinating site for the COVID-19 pandemia in Italy), Prof. Giuseppe Ippolito.

It will be a randomised open study with three parallel arms, empalumab or anakinra as add-on therapy to Standard of Care, to be compared to Standard of Care only.The study will comprise up to 54 patients and cover a treatment duration of 2 weeks. The assessment will follow a step-wise approach which will be described in the protocol.

The CTA includes:

- The CTA Form
- The Clinical Study Protocol
- The Patient Information and Informed Consent
- The already existing IB for emapalumab (supporting HLH indications)
- SmPC for Kineret, USPI for emapalumab
- The labelling of the IMPs

The clinical trial will be submitted for review by the Ethics Committee.

It should be noted that due to the urgency of the situation, the Sponsor has for this protocol requested exemptions to what is required for a Clinical Trial Application and when conducting a clinical trial:

1) An IMPD has not been established. However, Kineret is approved centrally in the EU/EEA since March 2002 (SmPC enclosed). Emapalumab was approved by the FDA for primary hemophagocytic lymphohistiocytosis (pHLH) in November 2018 (USPI enclosed). Further, clinical trials with emapalumab to document the pHLH indication (Protocols NI-0501-04, -05 & -09) have previously been approved in Italy. The batch planned for the current study is the same which was used for Protocols NI-0501-04, -05 in Italy, with the study specific labelling adjusted.

   Please note that for emapalumab, the same IMPD will be used as for study NI-0501-09 (NI-0501 IMPD Part 3 – November 2017). The QP certification site will be ABF Pharmaceutical Services GmbH, Gastgebgasse 5-13, 1230 Vienna, Austria or Swedish Orphan Biovitrum AB (publ), the latter being an addition in comparison to the IMPD. The packaging site will be ABF or Rechon, PO Box 60043, Soldattorpsvägen 5, SE-216 10 Limhamn Sweden, the latter also being an addition in comparison to the IMPD.

2) Contract negotiations with hospitals is a time consuming process and it will not be possible to finalise this in time for start of the study. The principal investigators at each site will however be required to sign the Clinical Study Protocol.

3) SAEs and AEs will be collected according to instructions in the protocol, in short:

   a. All fatal and life-threatening SAEs occurring after study drug (emapalumab, anakinra) initiation or after randomisation to Standard of Care must be reported on an SAE form to the company and on AE pages in the CRF.
   b. Non-serious AEs *of special interest*, as defined in the protocol, will be recorded only in the CRF.
   c. Abnormal laboratory findings, if serious (fatal or life-threatening), must be reported on an SAE form to the company and on AE pages in the CRF. Certain lab values are however not required to be reported as SAEs as defined in the protocol.

We will follow Directive 2001/20/EC, Article 17 1(a) and shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening will be reported to competent authorities and to the concerned Ethical Committees within seven days. We will not be able to comply with Article 17(b) for all other suspected serious unexpected adverse reactions to be reported within fifteen days since they will not be collected.

Based on the known safety profile of emapalumab and Kineret, the sponsor is of the opinion that their administration in the unapproved indication of COVID-19 infection would not pose additional risk to subject safety compared to normal clinical practice.

4) The Sponsor will establish a risk-based approach to monitoring and, considering the current situation, will need to utilize remote monitoring only during study conduct.

   To ensure ongoing subject safety and well-being, and control risks to study critical processes, such as review of informed consent forms and primary efficacy variables, alternative mechanisms of oversight will be introduced (such as phone calls, video calls etc). The Sponsor will also investigate if other measures for sharing data can be implemented, e.g. sharing de-identified source documents in shared drives/locations.

5) CV:s for the prinicpal investigator at each site will be collected, but not for the subinvestigators.

6) Information on experience of prior clinical trials and GCP training for the investigators will not be collected.

7) Financial disclosure forms for the investigators will not be collected.

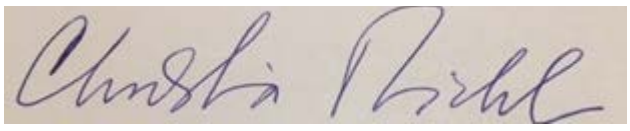
8) Delegation log on site will not be implemented.

9) A source data documentation log will not be established

10) A sample handling procedure will not be provided.

11) Laboratory accreditation will not be available at start of the study but collected later.

Looking forward to any comments AIFA may have.Yours sincerely,



Christina Rickhammar

VP Global Regulatory Affairs

Swedish Orphan Biovitrum AB (publ)