Sistema Socio Sanitario
Ospedale Papa Giovanni XXIII
Regione Lombardia
ASST Papa Giovanni XXIII

STUDY PROTOCOL

An observational case-control study of the use of siltuximab (SYLVANT) in patients diagnosed with COVID-19 infection who have developed serious respiratory complications

Investigational Medicinal Product:	Siltuximab (SYLVANT)
Indication:	COVID-19 patients who have developed serious respiratory complications
Phase:	This is an observational, case control study
Sponsor-Investigator:	Giuseppe Gritti, MD, PhD Hematology and Bone Marrow Unit, ASST Papa Giovanni XXIII Hospital
Institution:	Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy
Protocol Version and Date:	Final Draft v 0.9 16th March 2020

The study will be conducted according to the protocol as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the principles of the Good Clinical Practice in regard to protecting the safety and rights of the patients and with other applicable regulatory requirements.

2 SYNOPSIS

Title	An observational case control study of the use of siltuximab (SYLVANT) in patients diagnosed with COVID-19 infection who have developed serious respiratory complications
Developmental Phase	This is an observational case control study.
Institution	Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy
Study Centers	1 study center
Background	This observational study will collect data from patients treated under this already approved compassionate use program. The compassionate use programme was for treatment with SYLVANT siltuximab 400mg in patients diagnosed with COVID-19 infection who have developed serious respiratory complications. This observational study will group the patients into two cohorts receiving siltuximab. Patients in Cohort A are treated in a non-ICU setting and patients in Cohort B are in an ICU setting. Each patient will have a matched case control receiving standard treatment without siltuximab.
Objectives and Endpoints	• **Primary objective** *Cohort A:* reduction of the need of invasive ventilation or 30-day mortality *Cohort B:* reduction of mortality • **Secondary objectives** *Cohort A* Reduction of the need of time of ventilatory support Improvement of the lung function Improvement of radiologic findings *Cohort B* Reduction of days of need of intubation Percentage of patients that undergo to tracheostomy Improvement of the lung function Improvement of radiologic findings • **Primary endpoint:** *Cohort A***:** Reduction of the rate of need of invasive ventilation or 30-day mortality *Cohort B***:** Reduction of length of ICU staying or 30-day mortality • **Secondary endpoints:** *Cohort A* Reduction of days of need of ventilatory support Improvement of P/F fraction (resolution of ARDS i.e. P/F>300, or increase from baseline value of at least 50% if P/F >100 or 100% if P/F<100, at day 3, 8 and 15)

	Reduction of the duration of invasive ventilation or length of ICU Improvement of radiologic imaging *Cohort B* Reduction of days of need of intubation Percentage of patients that undergo tracheostomy Improvement of P/F fraction (resolution of ARDS i.e. P/F>300, or increase from baseline value of at least 50% if P/F >100 or 100% if P/F<100, at day 3, 8 and 15) Improvement of radiologic imaging • **Exploratory end points** Correlation of outcomes with IL-6 levels
Study Design	This is a single-center observational case control study in Italy that follows the use of treatment with siltuximab in patients with COVID-19 who have developed serious respiratory complications. Retrospective data collection will be carried out on those patients who have received the drug through the compassionate use program (this program is still ongoing, and enrolling patients). Patients receiving siltuximab that will be included into this observational study will be divided into 2 cohorts, and per current estimation split in a 3:1 ratio: 75% will be in Cohort A as not treated in an ICU setting and are not on mechanical ventilation, while 25% will form Cohort B and consists of patients in an ICU setting who are receiving invasive ventilation. Each patient will be matched to a consented case control patient receiving treatment other than siltuximab for their condition. *Match Criteria* Patients and controls will be matched according to the following criteria: • Age (by decades) • Sex (M/F) • P/F fraction (<100, 100-150 or >150) at baseline • Antiviral therapy Procedures outlined in this protocol are based on the compassionate use program, where patients are managed as per clinicians' best judgement and best practice. No clinical procedures are required by this observational protocol. Data on the procedures already performed during the routine diagnosis and treatment of COVID-19 patients will be collected. The list of clinical and laboratory parameters is provided to direct data collection for this observational study (as available in the medical records). During their hospitalization, patients will be monitored as per standard hospital practice or as per national (emergency) guidelines in accordance with extraordinary circumstances relating to the COVID-19 outbreak. After discharge, patients will be asked to provide (from their primary health care providers) relevant laboratory results for 30 days following start of COVID-19 treatment via ventilation (either mechanical or non-invasive).
Data Collected	Data collection for this study will be on the basis of existing medical records i.e. from standard practice tests at the hospital. The following data will be collected /recorded (if available): • Laboratory-confirmed COVID-19 test and date of diagnosis;

	• Other medical history; • Concomitant medications. The following data will be recorded from the time of first ventilation for 30 days (if available): • General information: o Hospital admission date; o ICU admission (if applicable); o Mobility; o Respiratory parameters; o Use of inotropic medication; o RR/MAP; o Diagnostic interventions (X-ray of thorax, computerized tomography [CT] scans); o Symptoms (fever, rash, abnormal cardiac function); o Mechanical ventilation; o Extracorporeal membrane oxygenation (ECMO). • Infectious Disease Parameters: o Inflammatory markers; o Peripheral edema; o Cytokine panel (full work-up pre- and post-treatment [serum]); o Pre-treatment C-reactive protein (CRP) levels; o Post-treatment CRP levels/24 h o Cardiac parameters/oxygen saturation; • General Disease Parameters: o APACHE II score; o Performance status (Eastern Cooperative Oncology Group [ECOG]/Karnofsky); o Laboratory assessments; o Virus titer; o IL-6 status: pre-treatment serum IL-6 levels (ELISA or similar approach, e.g. multiplex cytokine array); o Extended blood panel (hemoglobin/hematocrit [Hb/Ht]), thrombocytes (including peripheral blood mononuclear cell [PMBC]); o Coagulation status; o History of Human Immunodeficiency virus (HIV), Human herpes virus (HHV-8), hepatitis and tuberculosis infection.

Inclusion Criteria	Patients must meet the following criteria to be eligible to participate in the study: 1. Clinical and radiological diagnosis of pulmonary infection by COVID-19 2. Positive microbiological evidence of SARS-CoV-2 infection 3. Diagnosis of acute respiratory distress syndrome clinical panel in accordance with Berlin 2012 criteria 4. *For Cohort A only*: subjects are eligible if they are enrolled and treated within 48 hours from the beginning of NIV or CPAP 5. *For Cohort B only*: subjects are eligible if they are enrolled and treated within 48 hours from the beginning of invasive ventilation
Exclusion Criteria	Patients who meet the following criteria may NOT participate in the study. 1. Active infection of bacterial or viral (non COVID-19) origin
Number of Patients	Up to 50 patients: 50% receiving treatment (Cohort A and Cohort B) and 50% matched case controls.
Countries/Number of Sites	1 site in Italy
Statistical Methods	All data will be summarized using descriptive statistical analyses as appropriate. All data will be presented in by-subject data listings.

PROTOCOL APPROVED BY PRINCIPAL INVESTIGATOR

Name / Title: Giuseppe Gritti, MD PhD

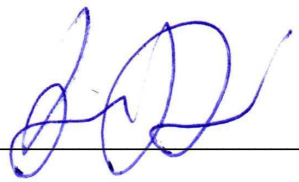
Address: P.za OMS 1, 24127 Bergamo

Contact Info: UOC Ematologia

I have read this protocol and agree to conduct the study as outlined herein, in accordance with the principles of the current Good Clinical Practices (GCP) in regards to protecting the safety and rights of the patients, the Declaration of Helsinki and complying with the obligations and requirements of clinical Investigators and all other requirements

I agree to inform all patients in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with ICH GCP and regulatory authority requirements.

I will be responsible for maintaining each patient's consent form in the study file and providing each patient with a signed copy of the consent form.

Signature  Date: _____17/03/2020_____

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	Adverse Event
ARDS	Acute respiratory distress syndrome
CRF	Case Report Form
CRP	C-reactive protein
CT	Computerized tomography
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ECMO	Extracorporeal membrane oxygenation
GCP	Good Clinical Practice
h	Hour
Hb	Hemoglobin
HHV-8	Human Herpes Virus-8
HIV	Human Immunodeficiency Virus
Ht	Hematocrit
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IL-6	Interleukin-6
ISO	International Organization for Standardization
MAP	Mean Arterial Pressure
N	Number
NIS	Non-Interventional Study
PBMC	Peripheral blood mononuclear cell
P/F	Peak flow
RA	Regulatory Authority
RR	Respiratory Rate
SAE	Serious Adverse Event
SD	Standard Deviation

5 INTRODUCTION

Coronaviruses (CoV) are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). A novel coronavirus (nCoV) is a new strain that has not been previously identified in humans (WHO).

One of the most serious potential symptoms that can occur with a coronavirus is the so-called 'cytokine storm' – when the immune system becomes over-stimulated and begins to attack a patient's own body. It has already been recognized that potential symptomatic treatment of critically ill COVID-19 infected patients should be directed towards reducing excessive immune response (A. Zumla, DS Hui et al.)

Medics already have considerable experience managing cytokine storms and excessive immune reaction with IL-6 blockers like tocilizumab. Roche has secured approval from China for its anti-inflammation drug Actemra (tocilizumab) to treat patients developing severe complications from coronavirus (COVID-19). In its latest treatment guidelines published online, the commission said that the biologic drug Actemra can now be used to treat coronavirus patients with severe lung damage and high IL-6 levels (Pharmaceutical-technology.com).

SYLVANT® (siltuximab) is a monoclonal antibody that prevents IL-6 from binding to IL-6 receptors and therefore causes blockade of IL-6 (EUSA Pharma UK).

In the Compassionate Use Program, critically ill COVID-19 patients (with a confirmed diagnosis) with severe acute respiratory distress will be treated with a single intravenous infusion of siltuximab (SYLVANT), Blocking of the excessive IL-6 could diminish the excessive immune response and consequently reduce its toxic effect on lungs. Early control of excessive immune response in acute respiratory distress syndrome may reduce mortality and might also ensure faster recovery with milder consequences.

This observational case control study will collect and analyze the data from patients who were treated under the compassionate use program (still ongoing). This study will assess the treatment effects of siltuximab in diagnosed COVID-19 patients with serious respiratory complications and could provide valuable insight into the development of treatments for patients with COVID-19.

5.1 Study Rationale

There is an emergency situation regarding treating patients with COVID-19 and especially those with lung complications and/or acute respiratory distress syndrome (ARDS), which is the main cause of morbidity and mortality in these patients. Siltuximab (SYLVANT) 400 mg is an approved product and dosage for idiopathic Multicentric Castleman Disease (iMCD): it is not indicated for the treatment of COVID-19 infection. However, due to observed clinical (lung dysfunction) and laboratory (high IL-6) presentation in COVID-19 patients, siltuximab (an IL-6 blocker) may potentially benefit patients who developed respiratory complication.

As siltuximab is being used for the first time in this indication, there is a requirement to collect and analyze efficacy and safety data from both the standard of care and siltuximab

treated patients in order to assess risk/benefit as well as the dosing regimen of siltuximab in this patient population. As this is an observational case control study, only available data will be collected and analyzed.

6 STUDY OBJECTIVES

The is a case control study to observe treatment and collect data on two cohorts of patients treated with siltuximab and a corresponding case control group of patients who have developed severe respiratory complications with COVID-19 infection.

Primary objective

Cohort A: reduction of the need of invasive ventilation or 30-day mortality

Cohort B: reduction of mortality

Secondary objectives

Cohort A

Reduction of the need of time of ventilatory support

Improvement of the lung function

Improvement of radiologic findings

Cohort B

Reduction of days of need of intubation

Percentage of patients that undergo to tracheostomy

Improvement of the lung function

Improvement of radiologic findings

Primary endpoint:

*Cohort A***:** Reduction of the rate of need of invasive ventilation or 30-day mortality

*Cohort B***:** Reduction of length of ICU staying or 30-day mortality

Secondary endpoints:

Cohort A

Reduction of days of need of ventilatory support

Improvement of P/F fraction (resolution of ARDS i.e. P/F>300, or increase from baseline value of at least 50% if P/F >100 or 100% if P/F<100, at day 3, 8 and 15)

Reduction of the duration of invasive ventilation or length of ICU

Improvement of radiologic imaging

Cohort B

Reduction of days of need of intubation

Percentage of patients that undergo to tracheostomy

Improvement of P/F fraction (resolution of ARDS i.e. P/F>300, or increase from baseline value of at least 50% if P/F >100 or 100% if P/F<100, at day 3, 8 and 15)

Improvement of radiologic imaging

Exploratory end points

Correlation of outcomes with IL-6 levels

7 INVESTIGATORS AND STUDY ADMINISTRATION STRUCTURE

Institution	Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy
CRO (responsible for data management, data analysis, data collection and monitoring)	To be define

Information regarding additional key personnel involved in the study, including names and contact details of participating physicians, technical departments and/or institutions, as well as information on members of additional study committees, can be found in the study files of the Institution and on site if required according to Institutions' standards.

8 OBSERVATIONAL PLAN

8.1 Overall Study Design and Plan – Description

This is a single-center, observational case control study in Italy that follows the use of treatment siltuximab in patients diagnosed with COVID-19 infection who have developed serious respiratory complications. Retrospective data collection will be carried out on patients who have received the drug through the compassionate use program. (this program is still ongoing, and enrolling patients).

Patients receiving siltuximab will be included into this observational study and will be divided into 2 cohorts, split in an approximate 3:1 ratio: 75% will be in Cohort A and are not in an ICU setting and are not on mechanical ventilation, while 25% will form Cohort B and consists of patients in an ICU setting who are receiving invasive ventilation.

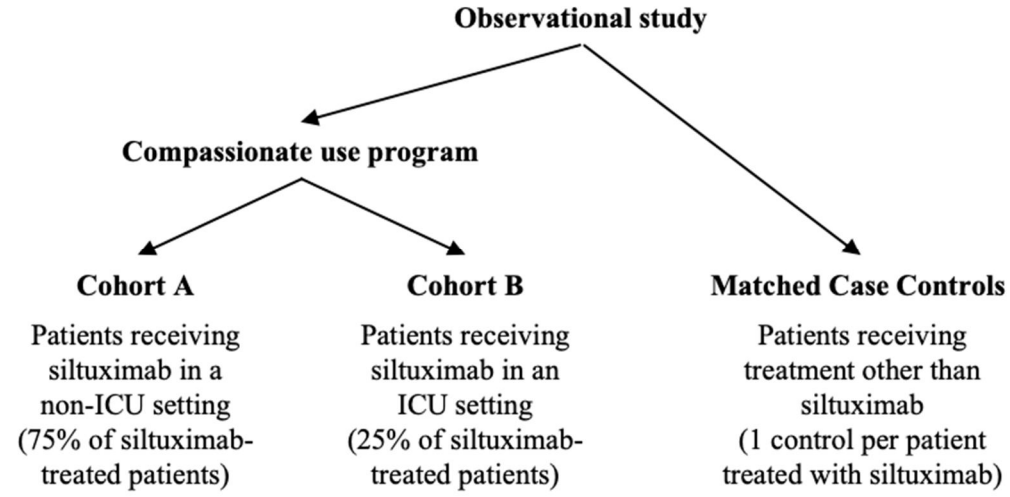
Each patient will be matched to a consented case control receiving treatment other than siltuximab for their condition.

Match Criteria

Patients receiving siltuximab and controls will be matched according to the following criteria:

- Age (by decades)
- Sex (M/F)
- P/F fraction (<100, 100-150 or >150) at baseline
- Antiviral therapy

Figure 1: Study Design



Procedures outlined in this protocol are based on the compassionate use program, where patients are managed as per clinicians' best judgement and best practice. No procedures are required by this observational protocol. Data on the procedures already performed during the routine diagnosis and treatment of COVID-19 patients will be collected. The list of clinical and laboratory parameters is provided to direct data collection for this observational study (as available in the medical records).

During their hospitalization, patients will be monitored as per standard hospital practice or as per national (emergency) guidelines in accordance with extraordinary circumstances relating to the COVID-19 outbreak. After discharge, patients will be asked to provide (from their primary health care providers) relevant laboratory results for 30 days following start of COVID-19 treatment via ventilation (either mechanical or non-invasive).

8.2 Justification of Study Design

The nature of the study allows for collecting information in a timely manner and will enable the researchers to generate hypotheses about the treatment under the compassionate use program for COVID-19. It is important to assess risk/benefit profile of siltuximab in this indication. A matched consented case control group (one case control per patient) has been included in this study to enable direct comparisons and to provide in-depth safety and efficacy data on siltuximab in the treatment of this patient population.

9 STUDY POPULATIONS

9.1 Eligibility

9.1.1 Inclusion Criteria

Patients must meet the following criteria to be eligible to participate in the study:

1. Clinical and radiological diagnosis of pulmonary infection by COVID-19
2. Positive microbiological evidence of SARS-CoV-2 infection
3. Diagnosis of acute respiratory distress syndrome clinical panel in accordance with Berlin 2012 criteria
4. For Cohort A only: subjects are eligible if they are enrolled and treated within 48 hours from the beginning of NIV or CPAP
5. For Cohort B only: subjects are eligible if they are enrolled and treated within 48 hours from the beginning of invasive ventilation

While approving this protocol, it is understood that the RA/IEC have approved collection and analysis of the data from deceased patients with COVID-19. See also protocol section 10.1.2.

9.1.2 Exclusion Criteria

Patients who meet the following criteria may NOT participate in the study.

1. Active infection of bacterial or viral (non-Covid-19) origin

9.2 Patient Identification

Each patient / data is identified by a unique identification code. This code is only used for study purposes for pseudonymization of the data. After informed consent, every person will be given a patient study number/code. The patient code consists of a observational study (Obs) code followed by the patient number (for example, the first patient enrolled would have the following number: XXX-001, second XXX-002, etc.). For the duration of the study and afterwards, only the patient's physician will be able to identify the patient based on the patient identification code.

Patient identification log will be set up to provide the link between the patient and their assigned study number. This document must be stored confidentially only at the Institution / site.

10 DATA COLLECTED DURING THE STUDY

All available data will be captured from medical records that will be generated by the treating physicians as per their standard practice i.e. no GCP requirements will be imposed on the medical records. See Section 10.1.1for information about the data collected that will be collected.

10.1.1 Tabulated Overview

All available data will be captured from medical records. The following data will be recorded (if available):

Laboratory-confirmed COVID-19 (Positive, validated RT-PCR Assay of nasopharyngeal swabs and ideally serum)
Demographics
Prior medications used
Past Medical History

The following data will be recorded from the time of first ventilation for 30 days (if available):

General Information
Hospital admission
ICU admission
Mobility
Respiratory parameters
Use of inotropic medication
RR/MAP
Rx (X-Thorax, CT scans)
Fever/rash/abnormal cardiac function
Mechanical ventilation
ECMO
Infectious Disease Parameters
Inflammatory markers
Peripheral edema
Cytokine panel- Full Cytokine panel workup pre and post treatment (Serum)
Pre-treatment CRP Levels
Post-treatment CRP Levels /24h
Cardiac parameters/Oxygen saturation
General Disease Parameters
APACHE II score
Performance status (ECOG/Karnofsky)

Laboratory Assessments
Virus titer
IL-6 status Pre-treatment Serum IL-6 levels (ELISA or similar approach, e.g.: Multiplex cytokine array)
Extended blood panel (Hb/Ht), thrombocytes, including PMBC
Coagulation status
History of HIV/HHV-8/Hepatitis/Tuberculosis infections

10.1.2 Enrollment/Initial Visit

Once a potential patient is identified for inclusion in the observational case control study, the physician will inform the patient about the study. This will include discussing the consent form and asking the patient, if possible, to read and provide consent. Where patient is able to provide only verbal consent (e.g. due to technical reasons, isolation) this consenting will be documented by the doctor who will complete the appropriate paperwork. When the patient is not able to provide consent due to their medical condition, consent for data collection / analysis will given by the doctor.

As COVID-19 is a highly contagious and easily transmissible virus, written consent may not be able to be sought from patients at enrollment. In the interests of human safety, in such circumstances only physicians will sign the informed consent, documenting in the doctor's emergency consent form also the circumstances under which consent was obtained.

Retrospective signed informed consent will be sought from patients when they are clear of the virus and no longer considered to have the potential to transmit COVID-19.

Once at least the doctors emergency consent form is available / there is basis for starting patient data collection and analysis, the physician or a delegate will use a CRF to document the patient's data. Data collection, regardless of type of contact, will follow a standard format and will be conducted equally for all patients.

10.1.3 Demographics

For demographic assessment, the following parameters will be recorded:

- Year of birth
- Gender

10.1.4 History of COVID-19 and Date of Diagnosis (Prior to Start of Treatment, if any)

- Virus Titer
- Positive, validated RT-PCR
- Assay of nasopharyngeal swabs
- Serum

- Other symptoms

10.1.5 Medical History and Concomitant Diseases

Medical history findings (i.e., previous diagnoses, diseases, surgeries, and conditions) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Considered relevant to the study

10.1.6 Concomitant Medication

Information on concomitant medication to be collected includes:

- Trade name or International Non-proprietary Name (INN)
- Start date
- Stop date or “continued”
- Daily dose, if applicable

10.1.7 Treatments

All treatments prescribed for COVID-19 and/or COVID-19 symptoms

- Trade name or INN and manufacturer
- Start date
- Stop date or “continued”
- Daily dose, if applicable

10.1.8 Signs and Symptoms

- Laboratory parameters (all laboratory parameters must include the value, the reference range [if available], and whether the value was considered Low or High [if available])
- Hospital admission
- ICU admission
- Mobility
- Respiratory parameters

- Use of inotropic medication
- RR/MAP
- Rx (X-Thorax, CT scans)
- Fever/rash/abnormal cardiac function
- Mechanically ventilated
- ECMO
- Infectious Disease Parameters
- Inflammatory markers
- Peripheral edema
- Cytokine panel - full cytokine panel workup pre and post treatment (serum)
- Pre-treatment CRP Levels
- Post-treatment CRP Levels /24h
- Cardiac parameters/Oxygen saturation
- General Disease Parameters
- APACHE II score
- Performance status (ECOG/Karnofsky)
- Laboratory Assessments
- Virus titer
- IL-6 status: pre-treatment serum IL-6 levels (ELISA or similar approach, e.g.: multiplex cytokine array)
- Extended blood panel (Hb/Ht) thrombocytes, including PMBC
- Coagulation status
- History of HIV/HHV-8/Hepatitis/Tuberculosis

10.2 Adverse Events

All SAE related to treatment with siltuximab during Compassionate Use should be reported as per the Compassionate Use Protocol (CUP). If during this study/retrospective data collection it is identified that the SAE's related to siltuximab treatment in COVID-19, or

associated with the disease recorded in the patient records, have not been reported, these must be reported within 24 hours as per the process in the CUP. Follow-up of all SAE's must be completed as per the CUP.

All non-serious AEs related to siltuximab treatment in COVID-19, or associated with the disease recorded in the patient records must be included in the CRF. For each AE, the severity, duration, action taken, and outcome of the event, will be documented in the CRF, if the information is available.

The Investigator will be responsible for reporting all relevant cases to the Regulatory Authorities and Ethics Committee under the CUP.

10.3 Premature Termination of Study/Closure of Site

The Institution has the right to close this study, and the physician has the right to stop recruitment, at any time.

11 STATISTICAL METHODS

In addition to statistical analysis described herein, the data may be reviewed intermittently to detect safety or efficacy signals in real time. Since this is an observational study, this data access will not affect the formal statistical analysis to be completed at the end of the study.

The statistical analysis will be performed separately in each study cohort to take into account the different endpoints defined for each study cohort. Also, within each study cohort, the analysis will include a descriptive comparison of the siltuximab treatment group and the control group with respect to the endpoints and other measurements.

11.1 Sample Size Determination

No statistical sample size estimation was performed. For this study patients from one single center in Italy will be enrolled as follows:

- All patients treated with siltuximab diagnosed with COVID-19 infection who have developed serious respiratory complications, and
- An equal number of case control patients that consented to their data collection.

It is estimated that in total up to 50 patients will be enrolled.

11.2 Statistical Considerations

The primary approach to the statistical analysis will be exploratory using descriptive statistics, exploratory tests and confidence intervals. All data will be presented in by-subject data listings.

11.2.1 Analysis of Demography, Disease Details, Pretreatment, Concomitant Medication, and Other Baseline Data

If not stated otherwise the following standard descriptive analyses will be presented:

11.2.1.1 Descriptive Statistics for Continuous Data

The number of patients (N), mean, standard deviation (SD), minimum, lower quartile, median, upper quartile, and maximum will be presented. These descriptive statistics will be determined for measured values and relevant differences.

11.2.1.2 Descriptive Statistics for Categorical Data

Absolute frequencies and percentages will be presented. For relevant changes from baseline, shift tables may be presented.

11.2.2 Analysis of Treatment Data

In addition to the descriptive statistics previously mentioned, all laboratory parameters will include the value, the reference range (if available), and whether the value was considered clinically significant or not (if available). All information related to COVID-19 and treatment will be presented.

11.2.3 Analysis of Endpoint Data

Data on the endpoints specific for the study cohort considered will also be analyzed by descriptive and exploratory statistical methods. Due to the small sample size statistical comparisons between the siltuximab treatment group and the matched control group will not be performed.

11.2.4 Analysis of Safety Data

Adverse Events and Serious Adverse Events will be reported using descriptive statistics.

11.2.5 Ad hoc Analysis

As soon as any relevant data has been recorded and based on the physician's decision on the basis of public interest, ad hoc analyses will be prompted, and information released in a timely manner.

12 DATA MANAGEMENT

12.1 Data Entry

The Institution will record the data from the patients' medical records onto CRFs and then transmit the pseudonymized data for analysis.

12.2 Case Report Forms

The study will be performed using CRFs, which will be completed for each patient.

12.3 Monitoring

The Institute will be responsible for data entry.

The Investigator will allow any regulatory agency to examine all study records, CRFs, corresponding patient medical records, and any other documents considered source documentation.

13 ETHICAL AND LEGAL ASPECTS

13.1 Independent Ethics Committee or Institutional Review Board

No additional investigations, above those specified in the compassionate use program and the standard of care, will be performed. In addition, patients will not be systematically allocated to treatments. All treatments observed in this study have been prescribed for an indication within the regular practice of the attending physician, independent of his/her participation in this study (non-interventional).

In Italy, where review by an Independent Ethics Committee (IEC) is required, documented approval from appropriate IEC will be obtained from the participating site prior to study start, according to local laws, regulations and organizations.

13.2 Ethical Conduct of the Study

This study is a non-interventional (observational) study. There is no assignment of a patient to a particular therapeutic strategy: the treatment decision has fallen within the scope of current practice and the compassionate use program, and the prescription of the medicines was clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring processes are required for participation or during the study. Epidemiological methods shall be used for the analysis of the collected data.

13.3 Regulatory Authority Approvals/Authorizations

The study will be carried out in accordance with guidelines of the European Medicines Agency, and applicable local law(s) and regulation(s).

Modifications to the study protocol will not be implemented by either the Institution or the physicians without prior agreement/approval from the Ethics Committee.

Non-interventional studies are explicitly outside the scope of Directive 2001/20/EC.

13.4 Patient Information and Consent

Before each patient is admitted to the study, informed consent will be obtained from the patient according to the regulatory and legal requirements of Italy. Owing to the highly contagious and potentially fatal nature of COVID-19, and in line with the 28 September 2012 Italian Bioethic Committee Guidance LA SPERIMENTAZIONE CLINICA IN PAZIENTI ADULTI O MINORI CHE NON SONO IN GRADO DI DARE IL CONSENSO INFORMATO IN SITUAZIONI DI URGENZA verbal consent may be obtained from the patient or if for medical reasons this is not possible from the patient, the Investigator should sign the doctor's emergency consent form in these cases Patients will be asked to retrospectively sign the informed consent form once they have been given medical clearance to do so; i.e., when they are considered virus-free. This consent form must be dated and retained by the Investigator as part of the study records.

13.5 Patient Insurance

Not applicable for this study.

13.6 Data Ownership

The Institute will be responsible for the custody of the data generated with this study and will ensure the confidentiality and safety of data. The physician is to retain records and documents pertaining to the conduct of this study including CRFs, source documents, and informed consent forms if applicable, for a period of at least 15 years after the study is closed.

13.7 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Institution.

As the study involves the collection and processing of personal data, the investigator must ensure that the anonymity of participating patients is maintained. On the CRF or other documents submitted the patients will be identified by a patient identification number only.

Documents generated for the purpose of the study i.e. patient identification log (see protocol section 9.2) and signed informed consent forms should be kept in a strictly confidential file by the Investigator.

As part of the required content of the informed consent, patients will be informed that their records may be reviewed by the RA / IEC.

The physician will maintain a list to enable patients' records to be identified in case of queries (patient identification log).

13.8 Record Retention

All CRFs and pertinent data, correspondence, original or amended protocol, all reports, and all other material relating to the study will be maintained securely in the Investigator's files.

13.9 Publishing and Study Reporting

The results of this study may be shared by the Institution or the Investigators with the public or presented at scientific meetings.

In addition, the Investigators and the Institution will comply with the requirements for publication of study results towards the RA/IEC after study completion.

Data presented in publications / study report will be anonymized

14 REFERENCES

A. Zumla, DS Hui et al. Reducing mortality from 2019-nCoV: host-directed therapies should be an option, The Lancet, Vol 395, Issue 10224, 35-36, Feb 22, 2020.

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Eusa Pharma UK. SYLVANT 400 mg powder for concentrate for solution for infusion Summary of Product Characteristics. Updated 21 January 2020.