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SURCOVID trial: A randomized controlled trial using convalescent plasma early during moderate COVID-19 disease course in Suriname

Study protocol version 1.2 (June 13th 2021)

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Brief Summary:

The new coronavirus pneumonia is an acute infectious pneumonia[1]. The pathogen is a previously unknown new coronavirus, namely 2019 new coronavirus (COVID-19)[2]. It has been found that the specific antibodies against virus antigen are produced after these patients were cured, could block the infection of COVID-19 on the host cells[3,4].

Summary

World knowledge about this virus is accumulating and data about the clinical presentation of infected patients is ongoing. Common known treatments, including ribavirin and interferon, however lack evidence. Although drugs with specific anti-coronavirus avidity have been identified, as yet only anti-inflammatory interventions for COVID-19 have been approved. Previous reports on other viral infections including SARS have suggested that convalescent plasma (CP) or serum is effective where no other treatment is available or in an emergency[5–7]. A meta-analysis by Mair-Jenkins and colleagues showed that the mortality was reduced after receiving various doses of CP in patients with severe acute respiratory infections, with no adverse events or complications after treatment[8]. Also initial responses from Wuhan after treatment of ICU patients with convalescent plasma therapy suggest that it may be a promising near-term therapy for patients with COVID-19 infection[3,9]. A recent study showed that early CP treatment is more effective than late CP treatment and that it prevents ICU level deterioration of the patient[10]. A recent ICU trial with CP produced by the Hemoclear method showed a strong treatment effect by a more than 70% reduction of mortality[11]. This was confirmed by similar findings in Iran ICU settings[12].

The primary objective of this study is to examine the effect of early convalescent plasma administration in the COVID non-ICU ward on clinical outcome[7]. The primary end point of the trial is the development of severe respiratory disease, defined as a respiratory rate of 30 breaths per minute or more, an oxygen saturation of less than 93% while the patient was breathing ambient air, or both. Secondary clinical end points are life-threatening respiratory disease, defined as oxygen supplementation at a fraction of inspired oxygen [Fio2] of 100%, noninvasive or invasive ventilation, admission to an intensive care unit, or any combination of these; ARDS (respiratory failure with a ratio of the partial pressure of oxygen to Fio2 ≤300 mm Hg, shock, multiple organ dysfunction syndrome, or any combination of these), and death associated with Covid-19, or one of the three secondary end points described above, alone or in combination. Patients in whom COVID-related illness is not resolved will be assessed for these end-point events until day 28 of trial participation.

Convalescent plasma donation. Following informed consent, blood will be collected from from patients who recently recovered from laboratory-confirmed COVID-19 infection for plasma isolation. Blood donation will occur at least 20 days following onset of disease in PCR-negative recovered patients who are still in hospital[13]. Whole blood (450 ml) will be collected from these donor-patients and bedside filtered into RBCs and convalescent plasma by a novel gravidity driven microfiltration device, Hemoclear. This allows direct reinfusion of the RBCs back to the donor-patients and also preventing significant RBC

loss during the procedure. Convalescent plasma will be processed and tested using the national standard plasma donation protocols.

CP treatment of patients. Following informed consent, patients with laboratory-confirmed COVID-19 who are admitted to the non-ICU ward with respiratory failure will be randomized into one of two groups: one group will receive 220 ml of convalescent plasma and the other group will receive a similar volume of NaCl 0.9%.

Patients will be followed up for evaluation of clinical outcome and collection of standard laboratory samples at day 0 (D0, immediately prior to infusion), 1, 3, 7, 14 and 28 of hospital stay after enrollment.

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Primary objectives

To evaluate the effect (decrease in hospital length of stay, MCU / ICU admission and length of stay, non-invasive and invasive ventilation, clinical parameters, laboratory parameters, radiological parameters and overall mortality) of convalescent plasma as add on therapy to our management of COVID-19 patients, which as of July 2020 also consists of dexamethasone, who are admitted in hospital to the COVID ward.

Study design

Study Type	Interventional (Clinical Trial)
Estimated Enrollment	210 participants
Allocation	Randomized 1:1
Intervention Model	Single Group Assignment
Masking	placebo-controlled
Primary Purpose	Treatment
Official Title	Clinical Study on the effect of COVID-19 convalescent plasma on clinical outcome of COVID-19 patients
Estimated Study Start Date	June, 2021
Estimated Primary Completion Date	October 2021
Estimated Study Completion Date	January, 2022
Location	Academic Hospital Paramaribo, Suriname

Benefits and nature and extent of the burden and risks associated with participation

Benefits of this study may include shorter stay in hospital and a decrease in mortality. The risks of plasma infusion are comparable to risks associated with regular blood transfusions. These include transfusion reactions and transmission of (unknown) transmittable diseases. Maximal precautions will be taken against these risks.

Planned Interim Analysis

An interim-analysis for efficacy and harm will be performed on the primary endpoint when 50% of patients have been included and have been followed-up for at least 30 days, with the use of predefined stopping rule as described in the protocol. An independent Data and Safety Monitoring Board (DSMB) will continuously have access to the data and shall be authorized, when indicated to advise the CMWO to discontinue or adjust the study protocol.

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Study Population

Patients with PCR confirmed moderate COVID19 disease, aged >18 years. These patients will be approached by the researchers or treating physicians for participation.

Criteria

Eligibility Criteria

Ages Eligible for Study	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study	All
Accepts Healthy Volunteers	No

Inclusion Criteria:

COVID-19 positive patients who have understood and signed the informed consent
Age ≥18 years
Hospital admitted patients with moderate COVID-19 to the non-ICU ward: Laboratory confirmed infection with COVID-19.

Exclusion Criteria:

Severe or Life threatening respiratory disease upon admission (the primary end point)
Viral pneumonia with other viruses besides COVID-19.
Ineligible for Convalescent Plasma Therapy
Participation in other studies.
Other circumstances in which the investigator determined that the patient is not suitable for the clinical trial
Refusal of informed consent study participation by Donor and/or Patient
Known IgA deficiency
Medical conditions in which receipt of 220 mL volume may be detrimental to the patient (e.g., decompensated congestive heart failure)
Females who are pregnant or breast feeding.

Donors: Eligibility for plasma donation

Donors will be approached by the researchers. The researchers will perform the screening in the Academic Hospital Paramaribo. Additional laboratory tests will be performed at the Medical Microbiology/Virology and Serology Laboratory of the Academic Hospital Paramaribo Suriname and if needed at the National Blood bank of Suriname. The threating physicians will be asked to contact the donors with the request if they may be contacted by the researchers.

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Inclusion criteria

- History of COVID infection that was documented by PCR
- Known ABO-Rhesus(D) blood group
- At least 20 days of illness passed
- Deemed fit for phlebotomy after physical examination
- Negative test results for National Blood bank screening panel for transfusion transmissible infections.

Exclusion criteria

- Age <18
- Heart failure stage I-IV (any cause)
- Chronic renal failure stage III-V
- Pulmonary hypertension

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Acquisition of convalescent plasma

Potential donors will have a medical examination by the principal investigator to evaluate phlebotomy fitness. Based on National Blood bank Suriname screening protocol, the plasma will be tested for absence of the following transfusion transmitted infectious diseases:

- Hepatitis B: HBsAg en HBV-DNA (NAT)
- Hepatitis C: anti-HCV en HCV-RNA (NAT)
- HIV: anti-HIV-1/2/(O) en HIV-RNA (NAT)
- Syphilis: RPR
- HTLV I/II: Anti-HTLV I/II
- *Trypanosomi cruzi* (Chagas disease).

Blood group (ABO-Rhesus) will be determined and the presence of irregular antibodies will be tested. Every plasma donor will have a unique label and number. When plasma is administered, this number will be registered in the patient file.
The Department of Medical Microbiology/Virology and Serology of the Academic Hospital Paramaribo Suriname shall, when available, screen plasma donors for the presence of IgM and IgG antibodies against SARS-CoV-2 using validated ELISA assays. Additional plasma and serum will be used for PBMC stimulation essays.

Convalescent plasma shall be acquired via plasmapheresis with use of Hemoclear® blood filters.
SARS CoV2 infection recovered patients will be tested according to standard blood bank protocol. Each patient will undergo one or two sessions of plasmapheresis in two weeks (depending on the number of donors available and antibody titers) at the Academic Hospital Paramaribo. Upon each session 1000 – 1500 mL of 1:1 diluted plasma will be obtained which will then be sent to the National Blood Bank of the Suriname Red Cross, Suriname, for processing. De convalescent plasma will then be sent to the Medical Microbiology/Virology and Serology Laboratory of the Academic Hospital Paramaribo Suriname for storage and distribution. Substitution for the donors consists of albumin 5 % (albumin 20 % diluted with NaCl 0.9%).
SARS CoV-2 antibody titers will be determined via validated semi-quantitatively ELISA methods. Plasma will be obtained only from COVID-19 recovered patients.

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Arms and Interventions

Arm	Intervention/treatment
Experimental: Treatment group/Convalescent plasma Drug/device: 220 ml convalescent plasma of cured patients obtained by ward produced by Hemoclear procedure and controlled by local bloodbank.	Standard care + infusion of 1*220 ml of COVID-19 convalescent plasma
	Biological: Convalescent plasma from patients who recently recovered from COVID-19 at least 20 days after primary illness.
Placebo Comparator: Control group	Standard care + infusion of 220 ml color coded NaCl 0.9%.

Two-hundred and twenty ml convalescent plasma will be infused over a period of at least 30 minutes. In order to immediately detect infusion reactions, patients will be closely observed during the entire time of plasma infusion, during which time and 1 hour thereafter, medication to treat anaphylaxis will be within hand reach.

Study procedures

Duration of treatment

Convalescent Plasma will be given once.

Duration of follow up

Until discharge or death before day 60.

Time of clinical evaluation

- Screening
- Baseline
- Day 3,5,7,10, 14 (only if still admitted in the hospital)
- At discharge or death or day 60 whichever comes first

Required investigations

Medical history

- Sex and age at hospital admission
- Date of first day of illness of SARS-CoV-2 infection
- Underlying medical illness at the time of first day of SARS-CoV-2 disease

- Concomitant medication used at the time of first day of SARS-CoV-2 disease
- Relevant comorbidities (which can attribute to development of a severe course of SARS-CoV-2 disease such as obesity, diabetes mellitus, hypertension, heart failure, chronic pulmonary diseases)

Physical examination

- Lowest measured oxygen saturation when breathing room air.

SARS-CoV2 classification

Moderate disease is defined as:

- Evidence of lower respiratory disease during clinical assessment or imaging
- Blood oxygen saturation ≥94%

Severe disease is defined as one or more of the following:

- Shortness of breath (dyspnea)
- Respiratory frequency ≥ 30/min
- Blood oxygen saturation ≤ 93%
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
- Lung infiltrates > 50% within 24 to 48 hours

Life-threatening disease is defined as one or more of the following:

- Respiratory failure
- Septic shock
- Multiple organ dysfunction or failure.

Hematology

- CBC, Absolute Neutrophil count (ANC), Absolute lymphocyte count, Fibrinogen, D-Dimer.

Blood chemistry

- ASAT, ALAT, GGT, AF, total bilirubin, LDH, CRP, Creatinin, Urea, Ferritin
- Additional sera for C3, C4, C1-esterase inhibitor and PBMC stimulation essays

Radiological examination

- Chest X-ray upon admission, 48 hours, 72 hours, day 5, 7, 10 and 14.

Withdrawal of patients or premature termination of the study

Withdrawal of individual patients from protocol treatment

Patients should be withdrawn from protocol treatment if any of the following criteria for withdrawal are met: Potentially life-threatening transfusion reaction during plasma infusion.

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can also decide to withdraw a patient from protocol treatment for urgent medical reasons. Patients who are withdrawn from protocol treatment will receive medical care according to local practice.

Follow up of patients withdrawn from protocol treatment

Patients who are withdrawn from treatment for other reasons than death will be followed as described. SAE information will be collected as described before.

Withdrawal of informed consent

If a patient states that he or she withdraws their consent to participate in the trial, the investigator shall attempt to verify the patient's intent and record this in the medical file of the patient:

- The patient can refuse further treatment and/or procedures according to protocol, while still consenting with further follow up data collection
- The patient can refuse further treatment and/or procedures according to protocol and withdraw consent for further follow up data collection.

Premature termination of the study

The treating physician or DSMB may decide to terminate the study prematurely based on the following criteria:

- There is evidence of an unacceptable risk for study patients (i.e. safety issue)
- There is reason to conclude that continuation of the study cannot serve a scientific purpose.

Above mentioned parties will promptly notify all concerned investigators, the ethics committee(s) and the regulatory authorities of the decision to terminate the study. They will provide information

regarding the timelines of study termination and instructions regarding treatment and data collection of enrolled patients.

Safety

Temporary halt for reasons of subject safety

The lead investigator or the DSMB will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The lead investigator will notify the accredited CMWO without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited CMWO. The investigator will take care that all subjects are kept informed.

AEs and SAEs

Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. AEs will be registered conform the local protocol of Academic Hospital Paramaribo.

Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- Results in death
- Is life threatening (at the time of the event)
- Requires hospitalization or prolongation of existing inpatients' hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgment by the investigator
- An elective hospital admission will not be considered as a serious adverse event.

The registration of SAE will be limited to the following:

- Death

- Life threatening transfusion reactions Serious Adverse Events (SAEs) will be reported from moment of plasma infusion according to protocol until 60 days following infusion
- The investigator will report the SAEs to the DSMB/METC without undue delay after obtaining knowledge of the events
- The investigator will report the SAEs to the accredited CMWO that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the investigators has first knowledge of the serious adverse events.

Follow-up of adverse events

All SAEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study, as defined in the protocol

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Endpoints

Outcome Measures

Primary Outcome Measures:

Development of severe respiratory disease, defined as a respiratory rate of 30 breaths per minute or more, an oxygen saturation of less than 93% while the patient was breathing ambient air, or both.

Secondary Outcome Measures:

- Clinical status assessed by the ordinal scale on days 0, 3, 7, and 15[Time Frame: up to 15 days]
- The differences in oxygen intake methods [Time Frame: up to 15 days]
    1. No need for supplemental oxygenation;
    2. Nasal catheter oxygen inhalation ;
    3. Mask oxygen inhalation ;
    4. Noninvasive ventilator oxygen supply ;
    5. Invasive ventilator oxygen supply.
- Duration (days) of supplemental oxygenation [Time Frame: up to 15 days]
- Duration (days) of mechanical ventilation [Time Frame: up to 15 days]
- The mean PaO2/FiO2 [Time Frame: up to 15 days] if applicable
- The detection frequency could be increased according to clinician's decision
- Time to COVID-19 negativity in respiratory tract specimens [every 3 days] [Time Frame: up to 15 days]
- Dynamic changes of COVID-19 antibody titer in blood [Time Frame: up to 15 days] The antibody titer is detected on days 0, 3 , 7 and 15
- Dynamic changes of IL-6 levels in blood [Time Frame: up to 15 days] The titer is detected on days 0, 3 , 7 and 15
- MCU / ICU admission
- Length of MCU / ICU (days) [Time Frame: up to 28 days]
- Length of hospital stay (days) [Time Frame: up to 28 days]
- All cause mortality [Time Frame: up to 28 days]

Statistical consideration

Statistical analysis

At the time of writing of this protocol, the available data suggested that some clinical or laboratory values may be associated with poor outcome (mortality). Of these, the following can be expected to be measured in almost all patients and will be taken into account in the statistical analysis: Age at admission, in ICU or not at the time of inclusion in the study, the highest value measured of CRP, LDH, Urea, Creatinin, CBC, neutrophil & lymphocyte count, fibrinogen, d-dimer, total bilirubin and the lowest oxygen saturation measured when the patient was breathing room air. For all these variables values will be used measured between hospital admission and before plasma transfusion. Students t-test and Chi-square tests will be performed to determine significance (defined as p value ≤ 0.05) when indicated.
If other as yet unknown variables are described in the medical literature, we may decide to include them as well by submitting an amendment to this protocol.

Interim efficacy and safety analysis

A pre-planned interim analysis for efficacy and harm will be conducted after 30 patients have been included and followed-up for at least 30 days.

Stopping rules

The study will be discontinued at the time of the interim analysis when a reduction in overall mortality is observed. Instead of the 60- day mortality endpoint, we will use the 30-day mortality endpoint for the interim analysis to allow for an earlier interim analysis.

Registration

Required regulatory and administrative documents must be provided to the CMWO before enrollment of the first patient.

Data collection and quality assurance

Case Report Forms

Data will be collected on printed forms to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints. Data collected on the forms are derived from the protocol and will include at least:

- Inclusion and exclusion criteria
- Baseline status of patient including medical history and stage of disease

- Timing and dosage of protocol treatment
- Any other parameters necessary to evaluate the study endpoints
- Survival status of patient

Each form will be identified by a trial number, and a combination of patient study number and hospital name. The form will be completed on site by the investigator or sub-investigator or an authorized staff member.

Data quality assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study center(s), review of protocol procedures with the investigator before the study.

Monitoring

An independent Data and Safety Monitoring Board (DSMB) of the Academic Hospital Paramaribo shall be appointed and will continuously have access to the data and shall be authorized, when indicated to advise the CMWO to discontinue or adjust the study protocol.

Ethics

Accredited Ethics Committee

The protocol will be submitted for approval to the National Ethics Committee (CMWO).

Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, the ICH-GCP Guidelines and applicable regulatory requirements. The site investigator is responsible for the proper conduct of the study at the study site.

Patient information and consent

In general, patients presenting at the participating hospital with the diagnosis under study and possibly qualifying for participation will be informed about the trial by the treating/attending physician and asked if they are interested to participate.

Written informed consent of patients is required before enrollment in the trial and before any study related procedure takes place. ICH-GCP and other applicable regulations must be followed in informing the patient and obtaining consent. It should be taken into consideration if the patient is capable of giving informed consent. Before informed consent may be obtained, the patient should be given ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the patient.

There is no set time limit for the patient to make a decision. The investigator should inform each patient if there is a specific reason why he/she must decide within a limited time frame, for example if patients condition necessitates start of treatment or if the trial is scheduled to close for enrollment.

The content of the patient information letter, informed consent form and any other written information to be provided to patients will be in compliance with ICH-GCP and other applicable regulations and should be approved by the ethics committee in advance of use. The patient information letter, informed consent form and any other written information to be provided to patients will be revised whenever important new information becomes available that may be relevant to the patient's consent. Any substantially revised informed consent form and written information should be approved by the ethics committee in advance of use. The patient should be informed in a timely manner if new information becomes available that might be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

Specific to this study protocol, patients admitted with COVID-19 infection will be informed about the study by the treating/attending physician who is involved in patient care of the patient. If the patient is interested, a member of the study team will visit the patient to inform him/her about the study. In case the patient is unable to give informed consent, the appropriate relative will be contacted and informed about the study and to give written informed consent.

Benefits and risk assessment

The risk of plasma infusion is comparable to the risk associated with regular blood transfusions. These include transfusion reactions and the transmission of as yet unknown infectious or other transmittable diseases. Precautions taken include, matching the donor and recipient for blood group, testing for infectious agents as well as testing for irregular antibodies in the donor.

Incentives

Patient will not be compensated for participation in the trial.

Administrative aspects and publication

Handling and storage of data and documents

Each patient is assigned a unique patient study number at enrolment. In trial documents the patient's identity is coded by patient study number as assigned at enrolment. The site investigator will keep a subject enrollment and identification log that contains the key to the code, i.e. a record of the personal identification data linked to each patient study number. This record is filed at the investigational site and should only be accessed by the investigator and the supporting hospital staff, and by representatives of the lead investigator or a regulatory agency for the purpose of monitoring visits or audits and inspections.

Patient confidentiality

Patient confidentiality will be ensured in compliance with hospital regulation.

Filing of essential documents

Essential Documents are those documents that permit evaluation of the conduct of a trial and the quality of the data produced. The essential documents may be subject to, and should be available for, audit by the inspection by the regulatory authority. The lead and co-investigators should file all essential documents relevant to the conduct of the trial on site. The lead and co-investigators will file all essential documents relevant to the overall conduct of the trial. Essential documents should be filed in such a manner that they are protected from accidental loss and can be easily retrieved for review.

Record retention

Essential documents should be retained for 25 years after the end of the trial. They should be destroyed after this time unless a longer record retention period is required by site specific regulations. Source documents (i.e. medical records) of patients should be retained for at least 15 years after the end of the trial. Record retention and destruction after this time is subject to the site's guidelines regarding medical records.

Storage and sharing of data

The forms will be stored in the department of Internal Medicine of the Academic Hospital Paramaribo Suriname for 25 years. Encoded data may be shared with other study groups for research purposes. If data are sent to countries outside de EU, patients confidentiality will be ensured at an equal level of EU regulation and the Dutch Act on Implementation of the General Data Protection Regulation.

Storage of samples

Biological samples should only be stored for the purpose of additional research if the patient has given consent. If no informed consent was obtained, samples should be destroyed after the patient has completed all protocol treatment and procedures. Storage of biological samples on site is subject to the site's guidelines. In this study 2 tubes of plasma will be collected and stored (after obtaining written informed consent) during admission and discharge for research purposes.
Samples that are shipped to another facility (e.g. a central laboratory) for a purpose as described in this protocol or for additional scientific research should be stripped from any identifying information and labeled with a code (trial name or number and patient study number as assigned at enrolment).

Amendments

A 'substantial amendment' is defined as an amendment to the terms of the ethics committee application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the patients of the trial
- The scientific value of the trial
- The conduct or management of the trial
- The quality or safety of any intervention used in the trial.

All substantial amendments will be submitted to the ethics committee and to the competent authority. Non-substantial amendments will not be submitted, but will be recorded and filed by the lead investigator.

Annual progress report

The lead investigator Rosita Bihariesingh will submit a summary of the progress of the trial to the accredited ethics committee once a year. The first report is sent one year after the first approval date of

the trial. Subsequent reports are sent annually until end of trial. Information will be provided on the date of inclusion of the first patient, numbers of patients included and numbers of patients that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

Temporary halt and (prematurely) end of trial report

The lead investigator will notify the accredited ethics committee and the competent authority of the end of the trial within a period of 90 days. The end of the trial is defined as the last patient's last visit.
The lead investigator Rosita Bihariesingh will notify the CMWO immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the lead investigator will notify the accredited ethics committee and the competent authority within 15 days, including the reasons for the premature termination.
Within one year after the end of the trial, the lead investigator will submit an end of trial report with the results of the study, including any publications/abstracts of the study, to the accredited ethics committee and the competent authority.

Publication policy

Trial results will always be submitted for publication in a peer reviewed scientific journal regardless of the outcome of the trial – unless the trial was terminated prematurely and did not yield sufficient data for publication.

Structured Risk Analysis

Potential issues of concern

The only concern is the concern that exists for the use of human blood products. No other concerns are in place

a. Level of knowledge about mechanism of action **See introduction**

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism. **See introduction**

c. Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material? **No**

d. Selectivity of the mechanism to target tissue in animals and/or human beings **Unknown**

e. Analysis of potential effect **See introduction**

f. Pharmacokinetic considerations **Unknown for SARS-Cov-2 antibodies at this time**

g. Study population **SARS-Cov-2 infected patients in the hospital**

h. Interaction with other products **None**

i. Predictability of effect **Not predictable at this time**

j. Can effects be managed? **Transfusion reactions are managed with standard transfusion reaction management protocols.**

Synthesis

All standard blood product safety measures are in place. The overall risk of a single allogeneic plasma transfusion is low. To reduce this risk further, we will only use plasma from male donors as the use of female donor plasma increases the risk for acute transfusion related lung injury. Given the mortality of the disease under study the risk is acceptable in our opinion

References

These are mentioned in the text.

Glossary of abbreviations

AE Adverse Event

CRP C-Reactive Protein

DSMB Data and Safety Monitoring Board

ECG Electrocardiogram

GCP Good Clinical Practice

Hb Hemoglobin

HIV Human Immunodeficiency Virus

ICH International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use

IMP Investigational Medicinal Product

LDH Lactate Dehydrogenase

CMWO Commissie Mensgebonden Wetenschappelijk Onderzoek

OS Overall Survival

PB Peripheral Blood

SAE Serious Adverse Event

SC Subcutaneous

SD Stable Disease

SUSAR Suspected Unexpected Serious Adverse Reaction

WHO World Health Organization