Clinical Study Protocol

Efficacy and safety of intravenously administered hzVSF-v13 in patients with COVID-19 pneumonia: a phase II, proof of concept, multicentre, randomized, parallel-group, double-blind, placebo-controlled study

Protocol Number: hzVSF_v13-0006

EudraCT Number: 2020-003614-13

Sponsor: ImmuneMed Inc.

Version Number: V1.0

28 July 2020

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1 STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable laws and regulations in force. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the competent Ethics Committee (EC)/Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard to the trial participants. All personnel involved in the conduct of this study have completed ICH GCP Training.

The protocol, informed consent form and all participant materials will be submitted to the EC/IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the EC/IRB before the changes are implemented to the study. All changes to the consent form will be EC/IRB approved.

2 PROTOCOL SUMMARY

2.1 SYNOPSIS

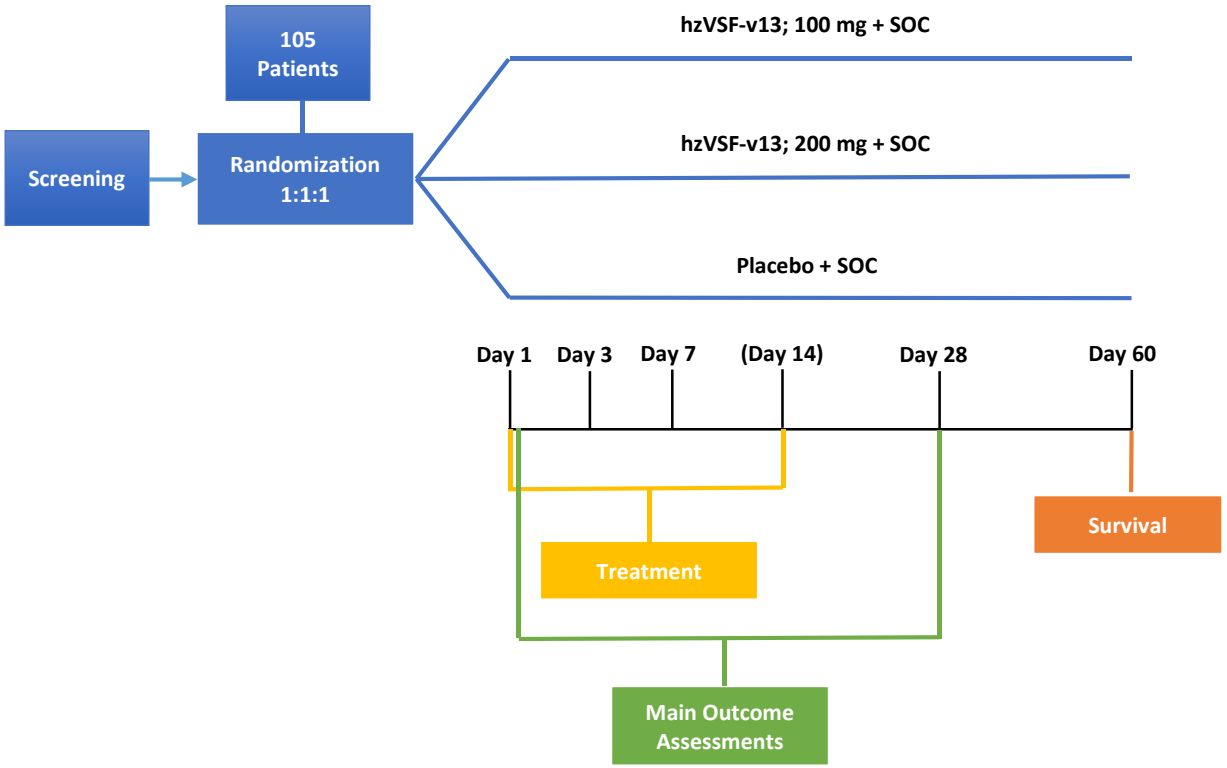
Title	Efficacy and safety of intravenously administered hzVSF-v13 in patients with COVID-19 pneumonia: a phase II, proof of concept, multicentre, randomized, parallel-group, double-blind, placebo-controlled study
Protocol Identification	Protocol Number: hzVSF_v13-0006 EudraCT Number: 2020-003614-13
Study Description	This is a phase II, proof of concept, multicentre, randomized, parallel-group, double-blind, standard of care (SOC) + placebo-controlled study. Patients must be at least 18 years of age with confirmed moderate-to-severe COVID-19 pneumonia as per World Health Organization (WHO) criteria including a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis of any specimen. At enrolment, patients may be on SOC according to local practice and local authority guidelines. Following informed consent, medications and eligibility criteria will be reviewed by the investigator or delegated staff. Eligible patients will be randomized and start treatment on the same day as screening or up to two days after completion of the screening procedures. Randomization will be stratified by patients in the intensive care unit (ICU) and patients not in ICU. Patients will be randomly assigned (1:1:1 ratio) to one of the following three treatment groups: • 100 mg hzVSF-v13 IV + SOC • 200 mg hzVSF-v13 IV + SOC • Placebo (saline) IV + SOC Patients will be followed until complete recovery (maximum 60 days). For patients who are discharged between treatment completion and Day 28 (main efficacy timepoint), the Day 28 visit may be conducted by telephone. The last visit will be held on day 60 and may be performed by telephone for discharged patients. Patients who discontinue treatment prematurely will be followed-up for survival status and for adverse events occurring until 30 days after the final dose of the study treatment.
Objectives	• To preliminarily investigate the safety and efficacy of two doses of hzVSF-v13 +SOC vs. placebo + SOC for the treatment of COVID-19 pneumonia. • To characterize the pharmacodynamic effects of the hzVSF-v13 doses.
Endpoints	**Safety endpoints** • Incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. • Change from baseline in vital signs and clinical laboratory test results. **Efficacy endpoints** • Clinical failure at Day 28, defined as any of:

	○ Death ○ Respiratory failure (patient is intubated) ○ Patient is in ICU • Clinical Improvement, defined as a decrease of at least 2 points on the WHO ordinal scale: 0. Uninfected: no clinical or virologic evidence of infection 1. Ambulatory: no limitation of activities 2. Ambulatory: limitation of activities 3. Hospitalized with mild disease: no oxygen therapy 4. Hospitalized with mild disease: oxygen by mask or nasal prongs 5. Hospitalized with severe disease: non-invasive ventilation or high-flow oxygen 6. Hospitalized with severe disease: intubation and mechanical ventilation 7. Hospitalized with severe disease: ventilation + additional organ support: vasopressors, renal replacement therapy, extracorporeal membrane oxygenation 8. Death • Time to clinical improvement, defined as the time from randomization to clinical improvement as described above. • Rate of overall survival at Day 28 and Day 60. • Cumulative mortality rate at Days 7, 14, 21, 28, and 60. • Time to hospital discharge or "ready for discharge" (i.e. normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen). • Ventilator-free days to Day 28. • Organ failure-free days to Day 28. • Duration of supplemental oxygen. • SARS-CoV-2 viral clearance over time through nasopharyngeal swab and bronchoalveolar lavage (BAL) samples (if available). **Pharmacodynamic endpoint** Serum tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and C-reactive protein (CRP) levels at baseline and at specified times after initiation of study drug. If available, the same assessments are to be performed in BAL samples.
Study Population	The study population will be made up of adult patients with confirmed moderate-to-severe COVID-19 pneumonia as per WHO criteria. **Inclusion criteria** 1. Signed written informed consent from any patient capable of giving consent, or, when the patient is incapable of doing so, by his or her legal/authorized representative. Note: In accordance with the European Medicines Agency (EMA) "Guidance on the management of clinical trials during the covid-19 (coronavirus) pandemic version 3 28/04/2020", if written consent by the trial participant is not possible (for example because of physical isolation due to COVID-19 infection), consent may be given orally by the trial participant in the presence of an impartial witness.

	2. Age 18 years or older. 3. Patient is currently hospitalized. 4. Diagnosis of COVID-19 pneumonia including a positive RT-PCR test for SARS-CoV-2 of any specimen and lung involvement confirmed with chest imaging (X-ray or computed tomography [CT] scan). 5. Able to comply with the study protocol. 6. Female patients must be postmenopausal (24 months of amenorrhea), surgically sterile or must agree to use an effective method of contraception throughout the study and for up to 120 days after stopping treatment. Effective contraception includes an established hormonal therapy or intrauterine device for females, and the use of a barrier contraceptive (i.e. diaphragm or condoms) with spermicide. **Exclusion criteria** 1. Patients with known or suspected hypersensitivity to hzVSF-v13 or to any of its excipients. 2. Active tuberculosis or suspected active bacterial, fungal, viral, or other infection (besides COVID-19). 3. Anti-rejection or immunomodulatory drugs within the past 3 months. 4. Absolute neutrophil count (ANC) <1000/µL at screening. 5. Platelet count < 50,000/ µL at screening. 6. ALT or AST >5 x upper limit of normal (ULN) within 24 hours at screening. 7. Serum creatinine >2 mg/dL (>176.8 µmol/L) or estimated creatinine clearance <30 ml/min measured or calculated by Cockroft Gault equation. 8. Pregnancy or breastfeeding. 9. Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (approved/investigational COVID-19 antivirals and other off-label drugs recommended by local health authorities are permitted). 10. Patients who in the opinion of the treating physician should not participate in this program (ex: severe acute respiratory distress syndrome [ARDS], septicaemia).
Description of Sites Enrolling Participants	The study will be conducted at approximately 6 centres and will involve approximately 105 patients.
Description of Study Intervention	**Investigational Medicinal Product (IMP)** hzVSF-v13 (humanized monoclonal immunoglobulin, IgG4) in 20 mM L-histidine / histidine hydrochloride, 250 mM sucrose, 0.02% (w/v) polysorbates (PS) 20, pH 5.8. Concentration: 40.0 ± 6.0 mg/mL in a 5 mL vial (200 mg/vial). **Placebo** 0.9% NaCl (normal saline) **SOC** SOC is according to local practice. The off-label use of drugs is limited to drugs recommended by local regulatory guidelines.

	Patients will be randomized (1:1:1 ratio) to one of the following study treatments: • 100 mg hzVSF-v13 IV + SOC • 200 mg hzVSF-v13 IV + SOC • Placebo (saline) IV + SOC In all three groups, patients will receive SOC and a single intravenous dose of one of the three study treatments on days 1, 3 and 7. One additional IV dose may be administered on day 14 in the absence of viral clearance. Each dose of study treatment is to be administered in 100 mL 0.9% NaCl with an infusion time of approximately 30 minutes. A 0.2 µm inline filter can be utilized for IV infusion.
Participant Duration	60 days (including telephone visit on Day 60)
Version and date	V1.0, 28 July 2020

2.2 SCHEMA


105
Patients
Screening
Randomization
1:1:1
hzVSF-v13; 100 mg + SOC
hzVSF-v13; 200 mg + SOC
Placebo + SOC
Day 1
Day 3
Day 7
(Day 14)
Day 28
Day 60
Survival
Treatment
Main Outcome
Assessments

2.3 SCHEDULE OF ACTIVITIES (SOA)

DAYS 1-28

Study days [§]	Screening -2 to 1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28[§]
Written informed consent	X																												
Inclusion/exclusion criteria	X																												
Demographics, medical history	X																												
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[1]	X																												X
Randomization		X																											
Complete physical examination	X																												X
Lung imaging[2]	X							X							X							X						X
ECG[3]	X														X														X
SARS-CoV-2 viral clearance[4]	X			X				X			X				X							X						X
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SpO_2[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PaO_2/FiO_2[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[6]	X	X			X			X			X				X							X						X
Clinical chemistry[7]	X	X			X			X			X				X							X						X
PT, aPTT	X	X			X			X			X				X							X						X
WHO ordinal scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
In-hospital outcomes[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Organ failure		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IL-1 β, IL-6, CRP, TNF- α	X	X	X	X	X	X	X	X			X				X							X							X
Study treatment[9]		X		X				X							X[9]														
Surgical and medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Survival		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

CRP = C-reactive protein; TNF = tumour necrosis factor, PT = prothrombin time, aPTT = activated partial thromboplastin time, PaO_2/FiO_2 = arterial oxygen partial pressure/fraction of inspired oxygen; SpO_2 = peripheral capillary oxygen saturation.

[§] If a patient is discharged prior to Day 28, all assessments listed for the Day 28/treatment discontinuation visit should be performed on the day of discharge. The day 28 visit (± 3 days) for these patients may be conducted by telephone to collect information regarding WHO ordinal scale, adverse events, concomitant medications and survival, whereas other assessments will not be performed. Patients who discontinue treatment prematurely are to be contacted to obtain survival status and to follow-up adverse events.

[1] A serum pregnancy test should be performed at screening and on Day 28 or day of treatment discontinuation

[2] Lung imaging (X-ray or CT scan) performed within 5 days prior to screening may be used for eligibility.

[3] ECGs should be performed weekly for patients receiving hydroxychloroquine as standard of care.

[4] Viral clearance assessed by nasopharyngeal swab and/or bronchoalveolar lavage. Results confirming positive SARS-CoV-2 virus by RT-PCR available within 7 days prior to screening may be used for eligibility.

[5] Vital signs (respiratory rate, heart rate, systolic and diastolic blood pressures and body temperature), oxygen saturation (SpO_2). For patients requiring supplemental oxygen, oxygen flow rate (L/min) and/or fraction of inspired oxygen (FiO_2) should be recorded. PaO_2/FiO_2 should be recorded if arterial blood gas is measured.

[6] WBC count, RBC count, haemoglobin, haematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[7] Bicarbonate or total carbon dioxide, sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, and ferritin.

[8] Start and end date of mechanical ventilation, hospital stay, ICU stay, supplemental oxygen, intubation or non-invasive ventilation (e.g. Continuous Positive Airway Pressure [CPAP], bi-level positive airway pressure [BIPAP], etc.).

[9] Treatment on Day 14 only in the absence of viral clearance. Patients are to be treated following an overnight fast of at least 10 hours.

[10] After informed consent, all adverse events are to be reported until 30 days after the final dose of the study treatment. After this period, only serious adverse events suspected of being related to study treatment are to be reported.

DAYS 29-60

Study days	Days 29-59*	Day 60#
Concomitant medications	X	X
Vital signs[1]	X	X
SpO_2	X	X
WHO ordinal scale	X	X
In-hospital outcomes[2]	X	X
Adverse events[3]	X	X
Survival	X	X

* Visits are to be performed daily and only for hospitalized patients.

For discharged patients, the Day 60 (± 3 days) visit can be performed by telephone call to collect information about survival, WHO ordinal scale, concomitant medications and adverse events. Other assessments are not performed.

[1] respiratory rate, heart rate, systolic and diastolic blood pressures and body temperature.

[2] Start and end date of mechanical ventilation, hospital stay, ICU stay, supplemental oxygen, intubation or non-invasive ventilation (e.g. CPAP, BIPAP, etc.).

[3] All adverse events are to be reported until 30 days after the final dose of the study treatment; after this period, only serious adverse events suspected of being related to study treatment.

3 INTRODUCTION

3.1 BACKGROUND AND STUDY RATIONALE

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and was first identified in December 2019 in Wuhan, China. Since then, it has spread rapidly, evolving into a full-blown pandemic. As of 30 June 2020, over 10 million cases of COVID-19 (according to the case definitions and testing strategies in the affected countries) have been reported worldwide, including over 500,000 deaths. The COVID-19 pandemic is posing an unprecedented threat to EU/EEA countries, the UK and Russia, which have been experiencing widespread transmission of the virus in their communities. In addition, there has been an increasing number of reports of COVID-19 outbreaks in long-term care homes across Europe with high associated mortality, highlighting the extreme vulnerability of the elderly in this setting. The absence of an effective treatment or a vaccine combined with an exponential growth in infections since late February led many countries to implement non-pharmaceutical interventions such as 'stay-at-home' policies (recommended or enforced) alongside other community and physical distancing measures such as the cancellation of mass gatherings, closure of educational institutions and public spaces (*ECDC, 2020*).

The clinical manifestations of COVID-19 are variable, and include asymptomatic carrier, acute respiratory disease, and pneumonia of varying degrees of severity. Asymptomatic cases are diagnosed based on positive viral nucleic acid test results, but without any COVID-19 symptoms such as fever, gastrointestinal, or respiratory symptoms, and no significant abnormalities on chest radiography. However, the transmission of SARS-CoV-2 through asymptomatic carriers via person-to-person contact has been observed in many reports. Patients with acute respiratory disease are laboratory-confirmed COVID-19 cases with respiratory symptoms; however, chest computed tomography (CT) does not reveal signs of pneumonia. Finally, patients with pneumonia are COVID-19 cases with both respiratory symptoms and pneumonia on chest radiography. This category includes severe pneumonia: either respiratory rate ≥ 30/minute, peripheral capillary oxygen saturation (SpO_2) ≤93%, or partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤300 mmHg, and a critical condition characterized by respiratory failure requiring mechanical ventilation, shock or other organ failure requiring intensive care (*Lai, 2020*).

COVID-19 is a viral-induced illness, whose outcome seems to be determined by the extent of a host immune system imbalance. The primary immune response is a positive response that leads to viral clearance in the majority of cases. However, for reasons that are still unclear, the secondary immune response may be exaggerated and challenge tissue integrity, in some cases leading to multiple organ failure, acute respiratory distress syndrome (ARDS) and death. This exaggerated response is known as a "cytokine storm", for which there is still no specific or effective treatment (*Sarzi-Puttini, 2020*).

3.2 hzVSF-v13

hzVSF-v13 is a humanized immunoglobulin (IgG4) with high specificity and affinity to vimentin expressed on the cell surface of virus-infected cells. hzVSF-v13 has a half-life of around 25 days in humans, resulting in a sustained effect. It has no antibody-dependent cell-mediated cytotoxicity, no complement-dependent cytotoxicity and its Fc receptor binding is weak, except with FcγRI.

Vimentin is the major component of the type III intermediate filament that maintains cytoplasm architecture and is critical during influenza virus infections as it facilitates endosomal trafficking, acidification and mediates viral genome penetration into the cytoplasm and propagation of infection (*Wu and Panté, 2016*). Furthermore, it was reported that cytoplasmic vimentin is translocated to the cell surface, where it interacts directly with the SARS-CoV spike protein during viral infection serving as a putative co-receptor involved in cell entry of SARS-CoV (*Yu et al., 2016*).

Mass spectrometry studies identified vimentin as the target protein that binds to hzVSF-v13 in virus-infected cells. As there was no binding to vimentin expressed by uninfected cells, it was postulated that hzVSF-v13 binds to vimentin when the latter has undergone structural changes induced by virus infection (virus-induced vimentin; vi-vimentin).

Immunohistochemical staining of hepatitis B virus (HBV)-infected and control liver tissues using virus suppressing factor (VSF) as primary antibody showed differences in vi-vimentin expression between normal cells and virus-infected cells, with higher expression and VSF binding in the latter. Moreover, in various human normal tissues, vi-vimentin was not identified by immunohistochemistry using VSF. Therefore, it was concluded that hzVSF-v13 does not bind or binds only weakly to vimentin in normal cells but binds strongly to vi-vimentin present in cells after viral infection.

Vimentin and vi-vimentin are considered to have distinct intracellular location and structure, and consequently different binding affinity to hzVSF-v13. Indeed, immunofluorescence staining of encephalomyocarditis (EMC) virus-infected and uninfected cells showed that vi-vimentin is found on the cell surface and has a “dot” shape that is distinct from the filament structure of vimentin seen in normal cells.

In vitro studies suggest that the differences in the three-dimensional structure of vi-vimentin compared to general vimentin might be due to post translational modifications of the protein occurring after viral infection.

Furthermore, hzVSF-v13 combined with a fluorescent dye was used to treat virus-infected cells, and observation of the hzVSF–vi-vimentin complex showed that hzVSF-v13 binds to vi-vimentin present on the cell surface of virus-infected cells, is internalized into the cytoplasm, fused with lysosomes and degraded.

The binding of hzVSF-v13 with vi-vimentin on EMC virus-infected cells activates the protein kinase B (Akt) signaling pathway, which is known to enhance the viability of host cells and inhibit viral replication. In addition, it was shown that VSF influences phosphorylation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) by reducing phosphorylation on Ser536, thereby inhibiting the NF- κB pathway. NF-κB is the upper signaling pathway of different inflammatory regulators. A decrease in inflammatory cytokines Interleukin (IL)-6, interferon (IFN)-γ and monocyte chemoattractant protein (MCP)-1 was observed when virus-infected cells were treated with VSF. A slight increase in IL-2, an immune activator known as growth factor of T cells, was observed suggesting that hzVSF-v13 does not induce a decrease in general immunity.

These observations indicate that hzVSF-v13 may cause the presentation of viral protein on the cell surface along with major histocompatibility complex (MHC) Class I, suggesting that inflammatory inhibition results from the regulation of related signaling pathways.

The changes in the signaling pathways induced by treatment with VSF were also observed in cells infected with influenza virus and HBV. There were partial differences depending on the types of cells and viruses, but

the increased phosphorylation of Akt and decreased phosphorylation of NF-κB by treatment with hzVSF-v13 were confirmed. These *in vitro* results were also confirmed *in vivo* in a mouse model of influenza.

3.2.1 NON-CLINICAL STUDIES

Pharmacodynamics

As mentioned previously, hzVSF-v13 binds to cellular receptor vi-vimentin, is absorbed through endocytosis and is metabolized and degraded by lysosomes. Binding of vi-vimentin induces changes in the activity of intracellular pathways, resulting in mediation of antiviral and anti-inflammatory activities. The majority of studies conducted so far demonstrated these activities against influenza and hepatitis B viruses. Two *in vitro* tests and one *in vivo* study investigated the potential antiviral efficacy of hzVSF-v13 against SARS-CoV-2 and betacoronavirus.

The *in vitro* efficacy of hzVSF-v13 to reduce viral titer in SARS-CoV-2-infected Vero cells was demonstrated together with a reduction in the expression of SARS-CoV-2 proteins in cells treated with hzVSF-v13. In the human colon epithelial cell line HCT-8, treatment of human betacoronavirus-infected cells with hzVSF-v13 reduced the expression of coronavirus proteins.

The *in vivo* study in human betacoronavirus-infected mice showed an increase in survival in infected mice treated with a single injection of hzVSF-v13 one day after infection. About 70% of mice survived with a single treatment of hzVSF-v13 at Day 1 post infection. The same applies to 60% of mice with repeated treatment of hzVSF-v13 at Day 3 and Day 5 post infection.

Mice, ferrets and dogs (beagles) were used to test the non-clinical antiviral and anti-inflammatory efficacy of hzVSF-v13 against influenza virus. Treatment at doses of 0.1 mg/kg to 2 mg/kg (1,000 U–20,000 U/kg) in influenza A virus-infected mice significantly suppressed viral-induced clinical symptoms and viral titer. hzVSF-v13 protected the ciliated epithelium, which is the main target of the virus and suppressed infiltration of immune cells (T cells and macrophages) to inhibit aggravation of pneumonia. Inflammatory cytokines were also decreased by treatment with hzVSF-v13 in this mouse model. The effective dose of hzVSF-v13 against influenza A virus in mice is around 0.5 mg/kg.

Ferrets were used as animal model to study the efficacy of hzVSF-v13 against influenza A infection as they show clinical signs similar to humans. Ferrets were intravenously administered 0.1 - 10 mg/kg of hzVSF-v13 on Days 1 and 3 after viral infection. Control ferrets with influenza infection presented destroyed ciliated epithelial cells and infiltration of immune cells in the lungs. In the treated groups, hzVSF-v13 effectively decreased viral titer in a dose-dependent manner, resulting in a reduced destruction of ciliated epithelia, infiltration of immune cells in the lungs and clinical signs of influenza. The effective dose of hzVSF-v13 in ferret models with influenza B infection was 1 mg/kg, which was comparable to the dose effective against influenza A. Moreover, the efficacy of hzVSF-v13, oseltamivir and their combination was investigated in influenza virus-infected ferrets. 0.4 mg of hzVSF-v13 at 1 day and 3 days post-infection showed similar anti-viral efficacy as 1.25 mg/Kg per day of oseltamivir. The combination treatment showed a synergistic effect in the reduction of viral titer.

In beagles, females were administered 0.5 mg/kg of hzVSF-v13 once intravenously 2 days after infection with influenza A. hzVSF-v13 inhibited viral titer in influenza A virus-infected beagle lungs and suppressed

pneumonia. As the VSF receptor was expressed in virus-infected lung tissue, this makes dogs a suitable model for assessing the activity of hzVSF-v13 against influenza.

The *in vitro* antiviral efficacy of hzVSF-v13 was demonstrated in cells infected with HBV. hzVSF-v13 was also effective against lamivudine-resistant HBV. Moreover, the administration of hzVSF-v13 in mouse hepatitis virus (MHV)-infected mice resulted in reduced degeneration of hepatocytes induced by MHV-2cc infection and in suppression of infiltration of immune cells due to inflammation. In a SCID/Alb-uPA mouse model with transplanted human hepatocytes, a reduction of HBV covalently closed circular DNA (cccDNA) was shown after administration of hzVSF-v13.

In woodchuck models of acute and chronic infection with woodchuck hepatitis virus (WHV), the anti-inflammatory effects of hzVSF-v13 were shown at doses over 1 mg/kg. Indeed, hzVSF-v13 suppressed levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and the recruitment of inflammatory macrophages and T cells in woodchuck liver tissue. The anti-HBV efficacy of hzVSF-v13 was also compared with tenofovir alafenamide fumarate in a woodchuck chronic hepatitis model. A synergistic effect of the combination concerning reduction of HBV cccDNA and WHsAg was demonstrated.

Safety pharmacology studies were conducted in order to evaluate the effects of intravenously administered hzVSF-v13 on the cardiovascular system, central nervous system and respiratory system. The investigational product was shown to have no effects when administered at doses of 6.25 and 25 mg/kg. Only in one animal treated with 100 mg/kg of hzVSF-v13 was a decrease in blood pressure, increase in heart rate, and a short PR interval observed, but the animal recovered within 24 hours after administration. No effects on the respiratory and central nervous systems were detected at the same dose.

In conclusion, pre-clinical studies performed with hzVSF-v13 did not raise any concerns regarding the safety of hzVSF-v13 and demonstrated its potential for the treatment of COVID-19-induced pneumonia, as well as of other viral infections including influenza A pneumonia and chronic hepatitis B.

Pharmacokinetics

I*n vivo* studies performed with hzVSF-v13 in mice, rats and dogs demonstrated that systemic exposure of hzVSF-v13 increased in a dose-dependent manner. Indeed, plasma levels of hzVSF-v13 increased proportionally to the increase in dose and to the increase in the frequency of administrations. Moreover, levels of hzVSF-v13 gradually decreased after treatment was stopped. However, in the 13-weeks repeated-dose experiments, hzVSF-v13 remained in blood for up to 8 weeks demonstrating slow elimination of the investigational product.

Anti-drug antibodies (ADAs) were observed in the blood of animals treated with hzVSF-v13, especially when the higher doses were administered. A concomitant rapid decrease of hzVSF-v13 levels in serum was observed in these animals.

Toxicology

hzVSF-v13 was essentially nontoxic in acute toxicity studies in rats with an approximate lethal dose considered to exceed the highest dose administered in the studies: over 100 mg/kg upon intravenous administration and over 80 mg/kg upon intramuscular administration.

Toxicity was evaluated in rats and beagles administered doses of 6.25, 25 and 100 mg/kg, 3 times a week for 2 weeks, for a total of 6 administrations. In rats, no toxicity was shown even at the high dose of 100 mg/kg. Therefore, the no observed adverse effect level (NOAEL) was determined to be over 100 mg/kg, which corresponds to a human equivalent dose (HED) of approximately 16.2 mg/kg in a 60-kg adult subject, 972 mg in total. In beagles, symptoms such as hypoactivity, vomiting, paleness or hyperemia appeared on the 6th administration of 25 mg/kg and the 4th administration of 100 mg/kg. All symptoms resolved within approximately one hour and were considered hypersensitivity reactions due to the immunogenicity of the test substance. Moreover, the size of the germinal center of the spleen was increased in all test substance groups of both sexes. This finding was considered a normal immune reaction due to the immunogenicity of the test substance and was reversible. The hypersensitivity reactions seemed to be caused by the formation of ADAs to hzVSF-v13, but this is unlikely in humans. From these results, the NOAEL of male and female beagles was considered 6.25 mg/kg. However, as the test substance is a humanized immunoglobulin that can be immunogenic in dogs, the NOAEL was considered 100 mg/kg excluding the above-mentioned hypersensitivity reactions. This corresponds to an HED of approximately 54.1 mg/kg in a 60-kg adult subject, 3246 mg in total.

In addition, toxicity was evaluated in rats and beagles administered doses of 2, 6 and 18 mg/kg, 3 times a week for 13 weeks, for a total of 39 administrations. No toxicity was shown in rats in all dose groups. Therefore, the NOAEL was determined to be over 18 mg/kg. This corresponds to an HED of approximately 2.92 mg/kg in a 60-kg adult subject, 175.2 mg in total. No symptoms were seen in male or female beagles in the 2 and 6 mg/kg dose groups. However, in the 18 mg/kg dose group, symptoms related to hypersensitivity such as decreased activity, pallor, and vomiting were seen in 2 out of 5 cases of males on the 13th day (6th administration), and mild hypersensitivity symptoms including decreased activity, vomiting, pallor, erythema, hyperemia, lethargy, and edema occurred in 1 out of 5 cases of females on the 10th day (5th administration) and 3 out of 5 cases of females from the 41st day. Based on these results, the NOAEL was considered to be 18 mg/kg if the aforementioned hypersensitivity reactions are excluded, since these hypersensitivity reactions were relatively mild, and the investigational product is a human-derived antibody that can be immunogenic in dogs. This corresponds to an HED of approximately 9.7 mg/kg in a 60-kg adult subject, 582 mg in total.

The highest therapeutic dose so far administered to humans was 1200 mg, which represents a dose level of 20 mg/kg body weight in a 60-kg adult patient.

Finally, good local tolerance was observed in all toxicity studies performed.

No information on reproductive toxicity, genotoxicity and carcinogenicity is available.

In conclusion, an overall favorable risk-benefit profile of hzVSF-v13 for the proposed doses to be tested in clinical trials and the intended therapeutic use in humans can be evidenced.

For details, see the Investigator's Brochure (IB).

3.2.2 CLINICAL STUDIES

Human data come from a phase I study in healthy volunteers and from a compassionate use program conducted in Korea in patients with COVID-19 pneumonia.

The phase I study was a dose blocked-randomized, double-blind, placebo-controlled, single-dosing, dose-escalation study to investigate the safety, tolerability, pharmacokinetic characteristics of hzVSF-v13 after intravenous (IV) administration in healthy male subjects. Seventy-eight subjects were screened and 56 were randomized to receive either placebo (14 subjects) or one of the following ascending doses of hzVSF-v13: 10 mg and 20 mg (3 subjects each), and 50, 100, 200, 400, 800 and 1200 mg (6 subjects each).

The compassionate use program treated 7 patients with severe COVID-19. Patients were treated with intravenous hzVSF-v13 2 to 4 times within 2 weeks at a dose range of 50 mg to 200 mg.

Clinical pharmacology

Pharmacokinetic data is related to the phase I study in healthy volunteers described above. In this study, a dose-proportional increase of serum concentration of hzVSF-v13 was evidenced, as well as a decrease in hzVSF-v13 serum concentration over time.

The median time to reach maximum blood concentration (T_{max}) after a single administration of hzVSF-v13 was 0.5 hr to 1.0 hr depending on the dose group, and the mean terminal elimination half-life ($t_{1/2}$) ranged from 367.59 hrs to 645.96 hrs except for the 10 mg group, in which the concentration was below the lower limit of quantification after 168 hrs in all subjects. The lowest $t_{1/2}$, excluding the 10 mg dose, was observed for the highest dose administered: 367.59 ± 132.90 hrs for the 1200 mg dose.

The maximum drug concentration in blood (C_{max}), the area under the drug blood concentration-time curve until the last quantifiable blood concentration (AUC_{last}) and the area under the drug blood-concentration-time curve up to infinity after administration (AUC_{inf}) increased in a dose-proportional manner. Mean C_{max} and mean AUC_{last} were observed within a range of 1.77 - 268.09 mg/L and between a range of 176.74 - 102677.10 h*mg/L, respectively, depending on the dose group. In addition, AUC_{inf} was observed within the range of 357.55 - 107035.24 h*mg/L.

Additional results from this study demonstrated a dose proportional increase in the 50 to 1200 mg dose range when a single dose of hzVSF-v13 was intravenously administered, excluding the 10 mg and 20 mg dose groups whose AUC_{extrap} exceeded 20%. The observed dose-proportional increase of drug exposure is comparable to pre-clinical results. Considering the relevant pharmacokinetic characteristics, a long half-life of about 15 to 26 days was shown, as expected from the preclinical studies.

No pharmacodynamic studies have been performed in humans. However, the pharmacodynamics of hzVSF-v13 were extensively investigated *in vivo* in pre-clinical studies and results are summarized in the paragraphs above.

Efficacy

The Efficacy of hzVSF-v13 for the treatment of COVID-19 pneumonia has not yet been formally investigated in a clinical trial. However, the potential of the investigational product for the treatment of COVID-19 pneumonia was shown pre-clinically in two *in vitro* tests and one *in vivo* study (see non-clinical paragraphs) as well as in a compassionate use program (CUP) conducted in Korea.

Seven COVID-19 patients with severe pneumonia were treated intravenously with hzVSF-v13 under the CUP run in Korea. Patients were treated between 25 February and 7 April 2020 with 2-4 doses that ranged from 50 mg to 200 mg per dose depending on the patient's medical conditions. Patients had a mean age of 59.2 ±

18.8 years (range: 29 – 81) and five were male. Six of the seven patients were under extracorporeal membrane oxygenation (ECMO) and/or mechanical ventilation. At the end of treatment, four patients (57%) were SARS-CoV-2 negative in pharyngeal swabs, and four patients showed clinical improvement based on radiologic findings, lower fever and decreased oxygen support. Two patients presented both negative swabs and clinical improvement. One patient was discharged after two doses and did not need to complete the full treatment plan (3-4 doses), whereas another patient discontinued treatment prematurely due to death from worsening of metastatic lung cancer.

Safety

The good safety profile of hzVSF-v13 was demonstrated in the phase I study mentioned above. Nineteen subjects (34.55%) reported a total of 52 treatment-emergent adverse events (TEAE), 48 of which (92.30%) were of mild severity. Three subjects experienced TEAEs of moderate severity: increases of blood creatine phosphokinase, hypertriglyceridemia and a laceration. No severe TEAEs or serious adverse events (SAE) were reported. Moreover, none of the TEAEs led to discontinuation from the study.

Overall, 42 adverse drug reactions (ADRs) were reported by 17 subjects (30.91%). Four ADRs collected from 3 subjects were of moderate severity, all the others were mild. Among the ADRs, five subjects (9.09%) reported a total of 7 TEAEs that were judged by the Investigator as being possibly related to the investigational product (the others were considered “unlikely related”). One subject (1.82%) in the 50 mg group had an increase in blood creatine phosphokinase, two subjects in the 1200 mg group (3.64%) reported somnolence, one subject in the 100 mg group (1.82%) had 2 headaches, and one subject in the 100 mg group (1.82%) had a maculo-papular rash and pruritus.

A total of 26 TEAEs were reported for the seven patients treated during the Korean CUP and all were considered not related or unlikely related to treatment with hzVSF-v13. Seven severe TEAEs were reported: creatinine increased, blood urea nitrogen (BUN) increased, anaemia, arrhythmia, lung consolidation, WBC increased and worsening of metastatic lung cancer. None of these events were judged by the Investigator as being related to the study product, except for anaemia, which was considered unlikely related.

The following serious adverse events were reported in the CUP in a total of three patients: haemoptysis, arrhythmia, candidiasis, lung consolidation, WBC increased, worsening of metastatic lung cancer (death), bacteraemia, pulmonary oedema and lung fibrosis. None of the events were related to treatment.

In the phase I study, no significant changes in hematology, blood chemistry, urinalysis and urine microscopy, vital signs, physical examination and ECG results were detected. A skin test for hypersensitivity reactions was also performed one day before infusion of the study product and no clinically significant results were reported.

As hypersensitivity reactions (formation of ADAs) were reported in dogs in preclinical studies, the immunogenicity of hzVSF-v13 was also tested in humans in the phase I trial. The results (presence of ADAs) for all subjects up to the 1200 mg dose were negative, meaning they were under a cut-off value (0.137) and thus no immunogenicity of the investigational product was observed up to this dose.

For details see the Investigator’s Brochure.

3.3 RISK/BENEFIT ASSESSMENT

3.3.1 KNOWN POTENTIAL RISKS

As described in the previous section, hzVSF-v13 can be considered safe when administered intravenously in humans at the doses undergoing testing in this study.

Indeed, at the hzVSF-v13 doses up to 1200 mg used in humans, the great majority of adverse events reported so far have been of mild or moderate severity. No severe or serious adverse events were reported in healthy volunteers treated with hzVSF-v13 in the phase I clinical trial at any of the doses tested. Severe and serious events were reported in COVID-19 patients treated with hzVSF-v13 in a compassionate use program, but none of the events was considered drug related.

The following adverse events considered possibly related to the study drug were reported among 5 of the 55 healthy volunteers treated in the phase I study: one subject in the 50 mg group had an increase in blood creatine phosphokinase, two subjects in the 1200 mg group reported somnolence, one subject in the 100 mg group had 2 headaches, and one subject in the 100 mg group had a maculo-papular rash and pruritus.

No drug-related adverse events were reported among the 7 patients participating in the CUP.

Drugs making up SOC each present their own risks. Please see the summary of product characteristics of each drug for information about risks and the management of drug-related adverse events.

3.3.2 KNOWN POTENTIAL BENEFITS

Although the efficacy of hzVSF-v13 for the treatment of COVID-19 pneumonia has not been formally tested in humans, the antiviral and anti-inflammatory activities of hzVSF-v13 have been clearly demonstrated in non-clinical studies and partially substantiated clinically in patients treated during a CUP.

The pathophysiology of severe acute respiratory syndrome induced by SARS-CoV-2 has similarities to that of severe community-acquired pneumonia caused by other viruses or bacteria (*Perrone et al., 2008; D'Elia et al., 2013*). The overproduction of early response proinflammatory cytokines (tumour necrosis factor [TNF], IL-6, and IL-1β) results in what has been described as a cytokine storm, leading to an increased risk of vascular hyperpermeability, multiorgan failure, and eventually death when the high cytokine concentrations are unabated over time (*Meduri et al., 1995*). Huang et al. reported the clinical features and cytokine profile of critically ill patients with COVID-19 in Wuhan, China, and suggested that a cytokine storm could be associated with the severity of disease (*Huang et al., 2020*).

Along with its proven pre-clinical antiviral activity against coronaviruses, influenza virus and hepatitis virus, hzVSF-v13 also reduces the release of proinflammatory cytokines through regulation of related signaling pathways. hzVSF-v13, with its antiviral activity and specific actions on the functions of proinflammatory cytokines to reduce cytokine storm and may thus represent a new treatment strategy for patients with COVID-19.

3.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

To date, therapeutic options for COVID-19 pneumonia remain limited. In light of the considerations stated above, we believe the potential benefits of this study outweigh its potential risks, and it is on these premises

that we propose to evaluate the efficacy and safety of intravenously administered hzVSF-v13 plus standard of care (SOC) compared with placebo plus SOC in patients with COVID-19 pneumonia.

4 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	ENDPOINT JUSTIFICATION
To preliminarily investigate the safety and efficacy of two doses of hzVSF-v13+ SOC vs. placebo + SOC for the treatment of COVID-19 pneumonia.	**Safety endpoints** ❖ Incidence and severity of adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. ❖ Change from baseline in vital signs and clinical laboratory test results. **Efficacy endpoints** ❖ Clinical failure at Day 28, defined as any of: • Death • Respiratory failure (patient is intubated) • Patient is in the Intensive Care Unit (ICU) ❖ Clinical Improvement, defined as a decrease of at least 2 points on the World Health Organization (WHO) ordinal scale: 0. Uninfected: no clinical or virologic evidence of infection 1. Ambulatory: no limitation of activities 2. Ambulatory: limitation of activities 3. Hospitalized with mild disease: no oxygen therapy 4. Hospitalized with mild disease: oxygen by mask or nasal prongs 5. Hospitalized with severe disease: non-invasive ventilation or high-flow oxygen	Safety endpoints are standard for clinical studies and reflect the identified potential risks involved in treatment with hzVSF-v13. As suggested in the WHO COVID-19 Therapeutic Trial Synopsis, 18 February 2020, the efficacy endpoints include composite measures of clinical improvement and/or survival assessed at a pre-specified time (28 days). As suggested by the WHO, endpoints include a separate endpoint of all-cause mortality and others that measure disease severity as well as biomarkers of illness such as viral clearance.

OBJECTIVES	ENDPOINTS	ENDPOINT JUSTIFICATION
	6. Hospitalized with severe disease: intubation and mechanical ventilation 7. Hospitalized with severe disease: ventilation + additional organ support: vasopressors, renal replacement therapy (RRT), ECMO 8. Death ❖ Time to clinical improvement (TTCI) defined as the time from randomization to clinical improvement as described above. ❖ Rate of overall survival (OS) at Day 28 and Day 60. ❖ Cumulative mortality rate at Days 7, 14, 21, 28, and 60. ❖ Time to hospital discharge or "ready for discharge" (i.e. normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen). ❖ Ventilator-free days to Day 28. ❖ Organ failure-free days to Day 28. ❖ Duration of supplemental oxygen. ❖ SARS-CoV-2 viral clearance over time through nasopharyngeal swab and bronchoalveolar lavage (BAL) samples (if available).	
To characterize the pharmacodynamic effects of the hzVSF-v13 doses.	Serum TNF-α, IL-1β, IL-6 and C-reactive protein (CRP) levels at baseline and at specified times after initiation of study drug. If available, the same assessments are to be performed in BAL samples.	

5 STUDY DESIGN

5.1 OVERALL DESIGN

This is a phase II, proof of concept, multicentre, randomized, parallel-group, double-blind, placebo + SOC-controlled study. Patients must be at least 18 years of age with confirmed COVID-19 pneumonia as per WHO criteria including a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) analysis of any specimen. At enrolment, patients may be on SOC according to local practice and local authority guidelines.

The study population will include both moderate and severely/critically ill patients. Severely/critically ill patients are defined as presenting at least one of the following:

- Respiratory rate ≥30 breaths/minute on room air.
- SpO_2 at rest ≤93% on room air.
- PaO_2/FiO_2 ≤300 mmHg.

Informed consent must be obtained from patients before any study related assessments or procedures are performed. Consent may be provided by the patient's legal/authorized representative should the patient be incapable of doing so. Following consent, medications and eligibility criteria will be reviewed by the investigator or delegated staff. Eligible patients will be randomized and start treatment on the same day as screening or up to two days after completion of the screening procedures.

Patients will be randomly assigned (1:1:1 ratio) to one of the following three treatment groups:

- 100 mg hzVSF-v13 IV + SOC
- 200 mg hzVSF-v13 IV + SOC
- Placebo (saline) IV + SOC

In all three groups, patients will receive SOC and a single intravenous dose of one of the three study treatments on days 1, 3 and 7. One additional IV dose may be administered on day 14 in the absence of viral clearance.

Patients will be followed until complete recovery (max. 60 days). For patients who are discharged between treatment completion and Day 28 (main efficacy timepoint), the Day 28 visit may be conducted by telephone. The last visit will be held on day 60 and may be performed by telephone for discharged patients.

Patients who discontinue treatment prematurely will be followed-up for survival status and for adverse events occurring until 30 days after the final dose of the study treatment. The study design is shown graphically in *Section 2.2*.

The study will be conducted at approximately 6 centres and will involve approximately 105 patients

5.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Randomized, double-blind, placebo-controlled trials represent the gold standard for clinical research. The design supports the rigorous assessment of the efficacy and safety of hzVSF-v13 combined with SOC.

The endpoints of the study and the 28-day study period are in line with the recommendations stated in the WHO COVID-19 Therapeutic Trial Synopsis, 18 February 2020.

5.3 JUSTIFICATION FOR DOSE

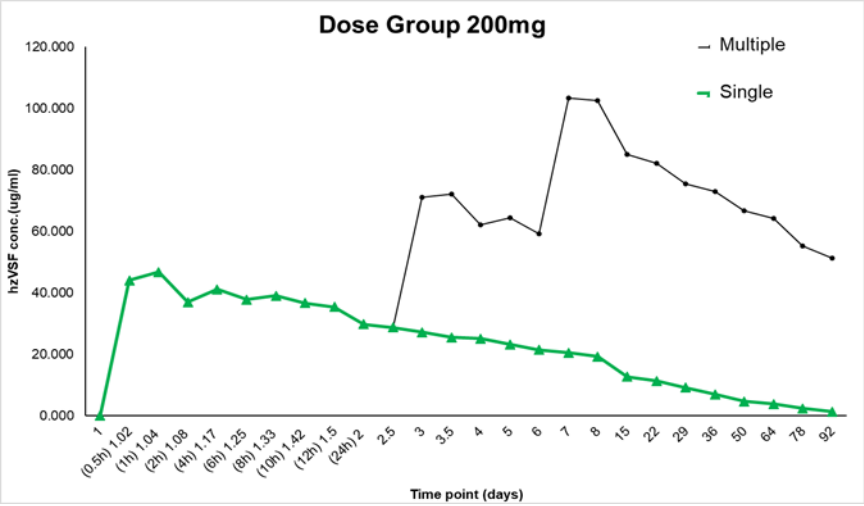
Two doses of hzVSF-v13 will be tested in this phase II clinical trial: 100 mg and 200 mg administered intravenously on Days 1, 3 and 7 plus standard of care. An additional dose may be administered on Day 14 in the absence of viral clearance. In the highest dose group, this represents a dose level of 3.3 mg/kg body weight for an adult patient with a standard body weight of 60 kg. Considering the dosing schedule for this clinical trial and the NOAEL (100 mg/kg) of the completed 2-week repeated dose studies where the investigational product was dosed 3 times a week, the calculated safety margin is approximately 4.86 in rats (2 weeks) and 16.23 in dogs (2 weeks). Moreover, in the phase I trial conducted in healthy volunteers, doses up to 1200 mg were well tolerated without dose-limiting toxicities.

hzVSF-v13 treatment suppressed the mortality of human betacoronavirus infected mice. About 70% of mice survived with a single treatment of hzVSF-v13 at Day 1 post infection. The same applies to 60% of mice with repeated treatment of hzVSF-v13 at Day 3 and Day 5 post infection. This result indicates that early treatment or repeated treatment of hzVSF-v13 increased the survival rate of mice.

Efficacy studies of hzVSF-v13 on SARS-CoV-2 infected Vero cells (kidney of an African green monkey) were performed. 10 and 100 μg/ml of hzVSF-v13 treatment decreased viral titer 59% (p-value=0.0671) and 92.5% ($p<0.001$) respectively, compared to control with Remdesivir (2 μM), which decreased viral titer 95.9%. Therefore, it is assumed that the multiple administration of doses of 100 mg and 200 mg (i.e. D1, D3 & D7) can achieve *in vivo* concentrations similar to those showing antiviral effects *in vitro*.

The efficacy of the selected doses of hzVSF-v13 for the treatment of COVID-19 pneumonia has not yet been formally investigated in a clinical trial. However, doses between 50 to 200 mg were administered to seven patients in a compassionate use program in Korea. The majority of patients (86%) were receiving ECMO and mechanical ventilation. Patients had underlying disease such as IgA nephropathy, hypertension, schizophrenia and metastatic pulmonary cancer. Four of the patients were SARS-CoV-2-negative after treatment with the investigational product and most of the others also showed signs of clinical improvement.

Simulation of the PK curve in the 200 mg group for multiple administration based on the PK result from the Korean Phase 1 Single ascending study shows that expected C_{max} is 103.3 μg/ml, expected AUC 149,690.8 μg·day/ml, and serum concentration at D29 would be maintained at 40μg /ml.



Considering non the clinical and non-clinical results mentioned above comprehensively, the selected doses in this Phase 2 study are expected to be clinically effective.

In conclusion, the doses selected thus present a good overall safety profile and will allow demonstrating the efficacy of the intended therapeutic use of hzVSF-v13.

5.4 JUSTIFICATION FOR STANDARD OF CARE

SOC is according to local practice. The off-label use of drugs is limited to drugs recommended by local regulatory guidelines.

5.5 JUSTIFICATION FOR COMPARATOR

SOC recommended by local regulatory guidelines + placebo is an appropriate control in this study given the lack of approved targeted treatment for COVID-19 pneumonia.

5.6 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all the scheduled procedures shown in the Schedule of Activities (SoA - *Section 2.3*). Patients will be followed up for a total of 60 days after the first dose of study medication. For patients who are discharged between treatment completion and Day 28 (main efficacy timepoint), the Day 28 visit may be conducted by telephone. The last visit will be held on day 60 and may be performed by telephone for discharged patients.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

6 STUDY POPULATION

The study population will be made up of adult patients with confirmed moderate-to-severe COVID-19 pneumonia as per WHO criteria.

6.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all the following criteria:

1. Signed written informed consent from any patient capable of giving consent, or, when the patient is incapable of doing so, by his or her legal/authorized representative. Note: in accordance with the European Medicines Agency (EMA) "Guidance on the management of clinical trials during the covid-19 (coronavirus) pandemic version 3 28/04/2020", if written consent by the trial participant is not possible (for example because of physical isolation due to COVID-19 infection), consent may be given orally by the trial participant in the presence of an impartial witness.
2. Age 18 years or older.
3. Patient is currently hospitalized.
4. Diagnosis of COVID-19 pneumonia including a positive RT-PCR test for SARS-CoV-2 of any specimen and lung involvement confirmed with chest imaging (X-ray or CT scan).
5. Able to comply with the study protocol.
6. Female patients must be postmenopausal (24 months of amenorrhea), surgically sterile or must agree to use an effective method of contraception throughout the study and for up to 120 days after stopping treatment. Effective contraception includes an established hormonal therapy or intrauterine device for females, and the use of a barrier contraceptive (i.e. diaphragm or condoms) with spermicide.

6.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients with known or suspected hypersensitivity to hzVSF-v13 or to any of its excipients.
2. Active tuberculosis or suspected active bacterial, fungal, viral, or other infection (besides COVID-19).
3. Anti-rejection or immunomodulatory drugs within the past 3 months.
4. Absolute neutrophil count (ANC) < 1000/µL at screening.
5. Platelet count < 50,000/ µL at screening.
6. ALT or AST > 5 x upper limit of normal (ULN) within 24 hours at screening.
7. Serum creatinine >2 mg/dL (>176.8 µmol/L) or estimated creatinine clearance <30 ml/min measured or calculated by Cockroft Gault equation.
8. Pregnancy or breastfeeding.
9. Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (approved/investigational COVID-19 antivirals and other off-label drugs recommended by local health authorities are permitted).
10. Patients who in the opinion of the treating physician should not participate in this program (ex: severe ARDS, septicaemia).

6.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing

requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event.

7 STUDY INTERVENTION

7.1 STUDY INTERVENTION ADMINISTRATION

7.1.1 STUDY INTERVENTION DESCRIPTION

Patients will be randomized to receive hzVSF-v13 or matching placebo solution plus SOC as described in *Section 7.1.2*.

Investigational Medicinal Product (IMP)

hzVSF-v13 (humanized monoclonal immunoglobulin, IgG4) in 20 mM L-histidine / histidine hydrochloride, 250 mM sucrose, 0.02% (w/v) polysorbates (PS) 20, pH 5.8.

Concentration: 40.0 ± 6.0 mg/mL in a 5 mL vial (200 mg/vial).

Placebo

0.9% NaCl (normal saline)

SOC

SOC is according to local practice. The off-label use of drugs is limited to drugs recommended by local regulatory guidelines.

7.1.2 DOSING AND ADMINISTRATION

Patients will be randomized (1:1:1 ratio) to one of the following study treatments:

- 100 mg hzVSF-v13 IV + SOC
- 200 mg hzVSF-v13 IV + SOC
- Placebo (saline) IV + SOC

In all three groups, patients will receive SOC and a single intravenous dose of one of the three study treatments on days 1, 3 and 7. One additional IV dose may be administered on day 14 in the absence of viral clearance.

Each dose of study treatment is to be administered in 100 mL 0.9% NaCl with an infusion time of approximately 30 minutes. A 0.2 µm inline filter can be utilized for IV infusion.

The following procedures should be followed for administering the study treatments:

Blinded site staff should administer the study treatment provided by the unblinded pharmacist on the same day as preparation:

a) Ensure the patient has completed an overnight fast of at least 10 hours.

b) The patient is to be placed in supine position.

c) A dedicated IV line should be used for administration.

d) A port line is not permitted.

e) Infusion of the treatment in 100 mL 0.9% NaCl is via a non-syringe infusion pump with inline filter over 30 minutes without interruption.

f) Flushing with normal saline prior to, and after infusion is required. After infusion, flush the line with normal saline at the same rate as the study treatment.

g) Infusion start time (time prior to beginning the initial flush of line), and infusion end time (time after final flush of line is complete), is to be documented in source documents and the eCRF. Reminder: Infusion should ideally be completed within 4 hours from the start of treatment preparation.

Destroy the used subject dose container as per local procedures and document destruction in source documents.

7.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

7.2.1 ACQUISITION AND ACCOUNTABILITY

hzVSF-v13 will be provided by the Sponsor. Placebo will be provided as 100 ml saline solution bags directly by the trial center and reimbursed by the Sponsor. Upon arrival of the study treatments at the site, the pharmacist and/or delegated staff should check for any damage and verify identity, quantity, integrity of seals and report any deviations. Upon receipt, the IMP must be stored according to the label instructions in a secured location. Designated staff will maintain accurate records of the product's delivery to the study site, the inventory at the site, the use by each patient and the return to the Sponsor or alternative disposition of unused products. Monitoring of drug inventory will be performed by the field monitor during the study conduct and a copy of the reconciliation log will be provided by the investigators upon completion of the study.

7.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

hzVSF-v13 will be supplied in glass vials sealed with a rubber stopper. The vials contain 5 ml of the IMP at a concentration of 40 ± 6 mg/mL. Placebo consists of 100 ml saline solution bags. The unblinded pharmacist will be receive the IMP labelled in the local language according to Annex 13 of Good Manufacturing Practice. Prior to clinical use, hzVSF-v13 (100mg or 200 mg) will be drawn into a syringe and injected in a 100 mL normal saline IV bag according to the pharmacy manual specifications. The 100 ml IV bag containing the IMP (100 mg or 200 mg) or only saline solution (placebo) will be labelled by the pharmacy to maintain blinding.

7.2.3 PRODUCT STORAGE AND STABILITY

Study treatments should be stored at +2 to +8 °C. The shelf-life of the IMP is 30 months (real time 18 months plus maximum 12 months). hzVSF-v13 is stable for 4 hours in both IV bags and syringes at ambient conditions, plus 30 minutes of infusion time.

7.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a randomized, double-blinded study. Patients will be assigned to one of three treatment groups (100 mg hzVSF-v13, 200 mg hzVSF-v13, placebo) in a 1:1:1 ratio.

Randomization will be stratified by patients in ICU and patients not in ICU.

In order to maintain blinded study conditions, pharmacy staff in charge of preparing and labelling the study treatments will be unblinded. Two study staff members, one under the supervision of the other, will prepare the study treatment. As soon as a patient is randomized, an email will automatically be sent to the pharmacist instructing him or her to prepare a 100 ml IV bag containing saline and hzVSF-v13 (100 mg or 200 mg) or only saline (placebo) for that randomization number.

The saline IV bag will be appropriately labelled by the unblinded pharmacist and delivered to the ward for administration. The pharmacist will then print and sign the email for filing purposes.

Details of the treatment preparation procedures are available in the Pharmacist's Manual.

Patient Numbering

Each patient will be identified in the study by a Patient Number that will be assigned when the patient is enrolled for screening and will be retained as the primary identifier for the patient throughout his/her entire participation in the study.

The investigator or designated staff will log on to the electronic case report form (eCRF) and provide the requested information to register the patients in the system. Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed. If the patient fails to be randomized, the reason will be entered on the Screening Disposition page.

Treatment Assignment/Randomization

Once the investigator or his/her delegate confirms that the patient fulfills all the inclusion/exclusion criteria, the Interactive Web Response System (IWRS) integrated into the eCRF system will assign the patient a randomization number linked to a treatment arm.

The patient randomization list will be generated through a validated SAS® program (SAS® for Windows release 9.4 - 64-bit) by an OPIS Statistician not involved in the study. The list will be uploaded into the eCRF system Clinical.NET.

Patients, investigator staff and all site personnel (except the pharmacist) will remain blinded to group allocation from randomization until database lock; randomization data will not be accessible by anyone involved in the study unless knowledge of the study treatment is relevant to the safety of the patient.

7.3.1 EMERGENCY UNBLINDING OF TREATMENT

Unblinding can be performed in case of emergencies to treat the participant.

If the investigator or authorized designee decides to break the code of a patient, it is suggested that the Monitoring Team (Medical Monitor or Clinical Research Associate) be consulted if possible before breaking the code, however this is not mandatory since the decision of the investigator cannot be influenced nor does it require the approval of the Monitoring Team.

Code breaking can be performed by the investigator or authorized designee (such as the Pharmacovigilance Department) at any time through the Code-break tool in the eCRF. In the unlikely case of system unavailability, the investigator can use the code break cards in sealed envelopes that will be available as backup for code breaking, whereas the Pharmacovigilance Department can have access to the randomization list.

If the code is broken, the investigator must record the date, time, and reason for breaking the code in the eCRF and must notify the Monitoring Team and the OPIS pharmacovigilance Department as soon as possible.

Emergency unblinding will cause the patient to be discontinued from the study.

Accidental unblinding will be dealt with on a case by case basis, if and when it arises. Patient data will continue to be collected according to the visit schedule, unless the patient withdraws consent.

7.4 CONCOMITANT THERAPY

All prior and concomitant medications or therapies administered within 60 days prior to screening will be recorded on the eCRF.

Along with SOC recommended by local regulatory guidelines, therapies considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, analgesics, etc.

7.4.1 RESCUE MEDICATION

In case of clinical failure of the study treatment, patients will be treated at the discretion of the investigator according to local practice and local regulatory guidelines.

7.5 DOSE MODIFICATION AND DOSE DELAY

Dose modifications and interruptions are not permitted except in the case of infusion related reactions (IRR) (see section below).

7.5.1 INFUSION RELATED REACTIONS

An IRR is defined as any adverse event that occurs immediately or within one hour after the infusion. This may include hypersensitivity or anaphylactic reactions. Delayed IRRs may however occur up to 1 Day post administration.

Signs of a possible infusion reaction are indicated in the table below.

Grade 1 (mild)	Headaches, fever, transient pruritis (itchiness), myalgia (muscle aches), flushing or low-grade temperature 37.5 – 38.0°C.
Grade 2 (moderate)	In addition to mild symptoms: chills/rigors, dizziness (without hypotension but postural hypotension may be present), hypertension, arthralgias (joint aches), chest tightness, urticaria (hives or itchy rash), fever > 38.0°C.
Grade 3 (severe)	Bronchospasm (wheezing, difficulty breathing or talking), angioedema (swelling of lips, tongue, larynx, face, abdomen, arms, legs).

Anaphylactic reactions are characterized by acute onset with typical skin features (urticarial rash or erythema/flushing and/or angioedema), PLUS involvement of respiratory and/or cardiovascular and/or persistent severe gastrointestinal symptoms, or any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present.

hzVSF-v13 infusions will be administered to patients at the site under close supervision. Health care professionals administering hzVSF-v13 infusions should be appropriately trained and able to recognize the symptoms associated with potential hypersensitivity reactions, including anaphylaxis, and should have the appropriate medication available for immediate use in case of severe reactions.

If an IRR occurs during infusion of the study treatment, the administration may be continued or discontinued at the discretion of the Investigator. The guidelines below are to assist the Investigator in managing possible IRRs:

Reaction	Action	Concomitant Medications to be given in sequential order
Grade 1 (Mild)	1. STOP infusion, call PI or RP immediate review 2. Check vital signs (temperature, BP, HR saturations every 15 minutes or as directed by PI until symptoms resolve)	In the case of recovery within 30 minutes after discontinuing treatment infusion without any intervention, reduce the infusion rate in half and complete the administration at the same visit. If no additional IRRs occur, proceed with the investigational product administration at the next visit over 30 minutes (±10 minutes).
Grade 2 (Moderate)	1. STOP infusion immediately and DO NOT recommence 2. Check vital signs (temperature, BP, HR saturations every 15 minutes or as directed by PI or RP until symptoms resolve) 3. Administer concomitant medications	1. IV hydrocortisone (helps mitigate the risk of delayed reaction which can occur 10-12 hours, up to 72 hours after administration). Check with PI if repeat doses are required 2. Promethazine 10mg, PO. Check with PI if repeat doses are required 3. Paracetamol 1g, PO (if specific symptoms such as headache, fever, chills and rigors are present)
Grade 3 -4 (Severe)	1. STOP infusion immediately and DO NOT recommence 2. Initiate emergency response call 3. Administer EPINEPHRINE WITHOUT DELAY 4. Further management as per the emergency response team	1. Epinephrine should be strongly considered in case of any concerns regarding anaphylactoid reactions (generalised pruritis, erythema, urticaria, angioedema) 2. Normal saline if hypotensive (5-10mL/kg over the first 5 minutes) 3. Salbutamol nebulised for wheezing. Apply oxygen 4. IV hydrocortisone 100mg 5. Paracetamol 1g, PO (if specific symptoms such as headache, fever, chills and rigors are present)
NB: If medications are required to manage symptoms of infusion related reactions then the infusion should not be recommenced. **In case of moderate to severe reactions, permanently discontinue study treatment.**		

8 TREATMENT DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1 DISCONTINUATION OF STUDY INTERVENTION

Study treatment can be discontinued by either the patient or the investigator. The reason for treatment discontinuation should be recorded on the eCRF.

Study treatment must be discontinued in case of:

- Participant decision
- Any situation in which study participation might result in a safety risk to the patient
- Adverse events, including laboratory findings, that in the opinion of the investigator preclude further treatment
- Following emergency unblinding
- Severe hypersensitivity reactions
- Pregnancy

8.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw their participation in the study at any time upon request.

Patients who discontinue treatment prematurely will be followed-up for survival status and for adverse events occurring until 30 days after the final dose of study drug. After this period, only serious adverse events suspected of being related to study treatment are to be reported.

The reason for withdrawal from the study should be recorded on the eCRF. Patients who withdraw or are withdrawn from the study will not be replaced.

8.3 LOSS TO FOLLOW-UP

Patients will be assessed in the hospital until complete recovery (max. 60 days). For patients discharged between the end of treatment and Day 28 (main efficacy timepoint), the Day 28 visit can be performed by telephone. The last visit will be held on day 60 and may be performed by telephone for discharged patients.

Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of loss to follow-up.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 EFFICACY ASSESSMENTS

A description of the assessments to be performed during the study is provided below. The specific timing of procedures/evaluations to be done at each study visit are captured in *Section 2.3*, Schedule of Activities (SoA).

9.1.1 SCREENING/BASELINE EVALUATIONS

Screening evaluations should be performed no longer than two days prior to randomization and include:

- Verification of inclusion/exclusion criteria.
- Patient demographics (age, sex, race).
- Medical history.
- Prior and concomitant medications.
- Surgical and medical procedures.
- Serum pregnancy test (to be repeated on Day 28 or day of treatment discontinuation).
- SARS-CoV-2 virus confirmation by RT-PCR if not already done within 7 days prior to screening.
- Complete physical examination. Limited, symptom-directed physical examinations may be performed at post-baseline visits as clinically indicated.
- Lung imaging (X-ray or CT scan): An imaging evaluation done within 5 days prior to screening is acceptable.

9.1.2 EFFICACY ASSESSMENTS

- Lung imaging

Lung imaging (X-ray or CT scan) should be performed at screening and then weekly during the 28-day assessment period.

- Vital signs/oxygen saturation and use

Vital signs (respiratory rate, heart rate, temperature, systolic and diastolic blood pressure) should be measured daily at the same time and in case of significant clinical changes.

For patients not on oxygen support, SpO_2 should be measured at the same time as vital signs. For patients requiring supplemental oxygen, oxygen flow rate (L/min) and/or FiO_2 should be recorded. PaO_2/FiO_2 should be recorded if arterial blood gas is measured.

- WHO ordinal scale

The WHO ordinal scale was developed by a special WHO committee to measure illness severity of COVID-19 over time and scores as follows:

0) Uninfected: no clinical or virologic evidence of infection
1) Ambulatory: no limitation of activities
2) Ambulatory: limitation of activities
3) Hospitalized with mild disease: no oxygen therapy
4) Hospitalized with mild disease: oxygen by mask or nasal prongs
5) Hospitalized with severe disease: non-invasive ventilation or high-flow oxygen
6) Hospitalized with severe disease: intubation and mechanical ventilation
7) Hospitalized with severe disease: ventilation + additional organ support: vasopressors, RRT, ECMO
8) Death

- Viral clearance

SARS-CoV-2 viral clearance is assessed through nasopharyngeal swabs and BAL (if available).

- In-hospital outcomes, consisting of the start and end dates of:
  - mechanical ventilation
  - hospital stay
  - ICU stay
  - supplemental oxygen
  - intubation
  - non-invasive ventilation (e.g. continuous positive airway pressure [CPAP], bilevel positive airway pressure [BIPAP], etc.)

9.2 SAFETY AND OTHER ASSESSMENTS

- Electrocardiogram

Standard 12-lead ECG assessments will be performed. Clinically significant abnormalities should be recorded on the eCRF.

- Haematology

WBC count, RBC count, haemoglobin, haematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

- Clinical chemistry

Bicarbonate or total carbon dioxide, sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase (ALP), ALT, and/or AST, uric acid, lactate dehydrogenase (LDH), and ferritin.

- Coagulation

Prothrombin time (PT), activated partial thromboplastin time (aPTT).

- Measures of inflammation

Serum TNF-α, IL-1β, IL-6 and CRP levels at baseline and at specified time points after initiation of study drug as indicated in the SoA. If available, the same assessments are to be performed in BAL samples.

9.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event can be defined as any untoward medical occurrence associated with the use of an intervention in humans after providing written informed consent for participation in the study until the end of study visit, whether considered intervention-related or not.

9.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3.3 CLASSIFICATION OF AN ADVERSE EVENT

9.3.3.1 SEVERITY OF EVENT

The severity of adverse events will be graded using the NCI CTCAE v5.0 Grades 1 to 5 will be used to characterize the severity of the event.

If NCI CTCAE v5.0 grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening and death related to the AE corresponding to Grades 1 - 5 will be used. Information about any deaths (related to an adverse event or not) will also be collected though a Death Form.

9.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another aetiology. There must be an alternative, definitive aetiology documented by the clinician.]

9.3.3.3 EXPECTEDNESS

The sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information described in the Investigator's Brochure.

9.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions will be captured on the eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator will record all reportable events with onset dates occurring any time after informed consent is obtained until 30 days after the final dose of study drug. After this period, only serious adverse events suspected of being related to the study drug are to be reported.

9.3.5 ADVERSE EVENT REPORTING

All identified non-serious AEs (related and unrelated) must be recorded and described on the eCRF.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion), or require changes in study medications.

Disease-related events such as disease progression (including fatal outcomes) should not be reported as adverse events.

9.3.6 SERIOUS ADVERSE EVENT REPORTING

Every Serious Adverse Event (SAE), regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to the Sponsor within 24 hours of site awareness.

Any SAE experienced after this 30-day period should only be reported to the Sponsor if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of

the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

Information about all SAEs will be reported using the SAE tool of the eCRF. In case of technical difficulties, SAE notification can be carried out by contacting the Contract Research Organization (CRO) OPIS in charge of Pharmacovigilance via email at all_phv@opis.it or by fax using the following number: Fax: +39 0362 633622.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study Sponsor and should be provided as soon as possible. The study Sponsor will be responsible for notifying Health Authorities of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than seven calendar days after the Sponsor's initial receipt of the information.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC and as per national regulatory requirements.

9.3.7 REPORTING EVENTS TO PARTICIPANTS

Should an event occur that changes the overall benefit/risk ratio of the study, the Sponsor shall evaluate if a risk minimization measure is needed. Should this measure require a substantial amendment to the protocol, the informed consent and patient information will be revised and submitted to the patient for written consent.

9.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

9.3.9 REPORTING OF PREGNANCY

The investigator shall report all pregnancy exposure occurring in a female patient or in a male patient's partner within 24 hours to the Sponsor using the Pregnancy Reporting tool of the eCRF. In case of technical difficulties, pregnancy notification can be carried out by contacting the CRO OPIS in charge of Pharmacovigilance via email at all_phv@opis.it or by fax using the following number: Fax: +39 0362 633622. The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy.

10 STATISTICAL CONSIDERATIONS

10.1 SAMPLE SIZE DETERMINATION

The total number of patients to be enrolled is approximately 105; 35 in each treatment group.

The incidence of clinical outcomes for patients with COVID-19 pneumonia may vary noticeably depending on patient baseline features and geographic area.

In the U.S., the American Centers for Disease Control and Prevention reported 31.4% hospitalizations and 11.5% ICU admissions (among patients with known hospitalization and ICU admission status) (*CDC COVID Response Team, 2020*). A report from the Gerontological Society of America states that rates of

hospitalization and death can reach 10% or more in the elderly *(Promislow, 2020*). A meta-analysis performed by Yinghao et al. found an incidence of patients requiring intensive care of 29.3% (0.190-0.395), an incidence of ARDS of 28.8%; (0.147-0.429) and a fatality rate of 6.8% (0.044-0.093) (*Yinghao et al., 2020*). A study by Grasselli et al. reports that ICU patients in the province of Lombardy, Italy, represent 16% of hospitalized patients with COVID-19 (n = 2217). According to the authors, the higher ICU admission rate than the ones reported in China are likely related to differences in the Italian population in terms of race, age, and comorbidities (*Grasselli et al., 2020*).

Consequently, estimating the rate of disease progression after hospital admission in patients treated with SOC cannot be done precisely.

Based on the range of available data, a sample size of 35 patients per treatment group should nevertheless be considered appropriate to obtain preliminary information on the safety profile and efficacy of hzVSF-v13.

In terms of clinical failure rate, if a true percent reduction of 50% for hzVSF-v13 + SOC versus placebo + SOC is assumed, then for each treatment group 35 patients will allow to estimate the corresponding odds ratio with the precision reported in the table below, where the estimate precision is expressed in terms of 85% Confidence Interval (CI).

Table: Estimate precision in each treatment group (35 patients) for different failure rates, 50% reduction in hzVSF-v13+SOC and 85% confidence level

Placebo + SOC failure rate (%)	hzVSF-v13 + SOC failure rate (%)	Percent reduction	Odds Ratio	85% CI for the Odds Ratio (Lower - Upper Limit)
40	20	50%	0.375	0.171 - 0.822
35	17.5	50%	0.394	0.174 - 0.893
30	15	50%	0.412	0.174 - 0.977

Estimates computed using nQuery version 8

No adjustment will be made for dropout rate because few dropouts and major protocol deviations are expected due to the disease and the study design.

10.2 POPULATIONS FOR ANALYSES

The following populations will be used for the statistical analyses:

- Safety set: all randomized patients who have received at least one dose of study treatment. Patients will be analysed according to the study drug actually received.
- Full Analysis Set (FAS): all randomized patients who have received at least one dose of study treatment. According to the Intention to Treat (ITT) principle, patients will be analysed according to the study drug assigned at randomization.
- Per protocol (PP): all randomized patients who have completed the study without any major protocol deviations. Patients will be analysed according to the study drug actually received.

10.3 STATISTICAL ANALYSES

10.3.1 GENERAL APPROACH

Continuous efficacy and safety data will be summarised with standard descriptive statistics (mean, standard deviation, median, minimum and maximum, 1st and 3rd quartiles). Categorical efficacy and safety data will be summarised by frequencies and percentages.

A detailed data analysis plan will be specified in a Statistical Analysis Plan (SAP).

The SAP will be written and signed off by the Sponsor and the OPIS Trial Statistician in advance of database lock. All analyses will be performed using SAS® version 9.4

10.3.2 ANALYSIS OF EFFICACY ENDPOINTS

Efficacy endpoints will be analysed on the FAS population. Analyses on the PP population will be performed as supportive.

Due to descriptive nature of the study, the inferential statistical tests will be used only for exploratory purposes. No multiplicity adjustments will be applied for multiple treatment comparisons.

- **Clinical failure**

A patient will be considered a clinical failure if on Day 28 the patient is dead, intubated and/or in ICU.

Patients who withdraw from the study before Day 28 will be considered as a clinical failure, unless there was no occurrence of death, respiratory failure or admission to ICU in all the available data and patients were discharged from the hospital.

The clinical failure rate will be descriptively analysed and the 85% CIs for each study treatment difference versus placebo + SOC will be provided together with the corresponding odds ratio.

In addition, a logistic regression model will be applied to assess the pairwise comparison of each hzVSF-v13 + SOC group versus placebo + SOC adjusting for the stratification factor (i.e. patients in ICU and patients not in ICU). The estimated odds ratio (OR) and the corresponding two-sided 85% CIs from the logistic regression analysis will be reported.

The analysis described for clinical failure will be repeated for each of the events that comprise the primary endpoint: occurrence of death, respiratory failure, and ICU admission. Separate logistic regression models will be fitted to compare the odds between treatment groups (each hzVSF-v13 + SOC group versus placebo + SOC group) for each of the events.

- **Clinical improvement**

Clinical improvement is defined as a decrease of at least two points on the WHO ordinal scale from the Day 1 visit to the Day 28 visit.

The clinical improvement rate at Day 28 will be presented using descriptive statistics together with the 85% two-sided confidence intervals and the odds ratio. The pairwise comparisons of each hzVSF-v13 + SOC group versus placebo + SOC will be assessed using a logistic regression model adjusted for the stratification factor.

The estimated odds ratio and the corresponding two-sided 85% CIs from the logistic regression analysis will be reported.

Moreover, the clinical status will be summarised by treatment group using descriptive statistics at each time point and change from baseline (Day 1) on the 9-point ordinal scale to Day 28. A pairwise comparison of each hzVSF-v13 + SOC group versus placebo + SOC will be carried-out using an ANCOVA model adjusting for the stratification factor and including baseline clinical status as a continuous linear covariate.

- **Time to clinical improvement**

Time to Clinical Improvement (TTCI), defined as the time from randomization until clinical improvement (i.e. a decrease of at least two points on the WHO ordinal scale), will be analysed using Kaplan-Meier methodology. Median with 85% confidence interval (CI) will be derived from the Kaplan-Meier curves.

- **Overall survival (OS)**

Overall survival (OS), defined as the time from randomization to the date of death due to any cause, will be analysed by means of Kaplan-Meier methodology. The estimated median and OS rate at Day 28 and Day 60 will be provided together with corresponding two-sided 85% CIs.

Moreover, hazard ratios will be estimated using the Cox proportional hazards model and presented together with 85% two-sided CIs.

The cumulative mortality rate at Days 7, 14, 21, 28, and 60 will be summarized descriptively. The difference in proportions for the treatment group comparison will be presented, together with an 85% CI.

- **Time to hospital discharge or "ready for discharge"**

Time to hospital discharge or "ready for discharge" (i.e. normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen) will be analysed using Kaplan-Meier methodology. The median value will be presented along with the 85% CIs.

Kaplan Meier curves for time-dependent variables will be compared using the Log-Rank Test and graphically plotted.

- **Other secondary endpoints**

The following secondary endpoints will be analysed descriptively:

- Ventilator-free days to Day 28 (calculated as number of days between randomization [Day 1] and day 28 with the patient alive without mechanical ventilation).
- Organ failure-free days to Day 28 (calculated as the number of days between randomization [Day 1] and day 28 with the patient alive without any organ failure).
- Duration of supplemental oxygen.
- SARS-CoV-2 viral clearance over time through nasopharyngeal swab and BAL samples (if available).

10.3.3 SAFETY, TOLERABILITY AND OTHER ANALYSES

Safety analyses will be conducted on the safety set and will be reported by actual treatment group.

Adverse Events

Adverse events will be assessed according to the NCI CTCAE v5.0.

The incidence of AEs will be tabulated by MedDRA System Organ Class and Preferred Term. The incidence of AEs will also be summarised by System Organ Class, Preferred Term, and severity (based on NCI CTCAE v5.0 grades). The same analysis will be repeated for SAEs regardless of treatment relationship, for treatment-related SAEs, AEs with NCI CTCAE v5.0 Grade 3 or 4 and for treatment-related AEs. AEs for which relationship to study treatment is not specified will be considered treatment related.

Deaths will be listed by patient and tabulated by reason for death.

Laboratory Parameters

Clinical laboratory data will be analysed descriptively by means of descriptive statistics and presented in the preferred unit of measurement (SI unit).

The following by treatment-group summaries will be generated separately for haematology and biochemistry:

- Change from baseline (Day 1) values to each time point (Day 7, 14, 21, 28).
- Shift tables using the low/normal/high/(low and high) classification to compare baseline (Day 1) to end of treatment (EOT) value.

Listings of all laboratory data and the classifications relative to the laboratory normal ranges will also be generated.

Other Safety Data

- Electrocardiograms (ECG) and vital signs results will be listed and summarized by treatment arm at each timepoint. Changes from baseline (Day 1) will also be calculated.
- The complete physical examinations performed at the screening and EOT visit will be summarized by study group.

Drug Exposure and Treatment Compliance

Duration of treatment, duration of observation and compliance will be summarized by treatment arm. The number of patients with dose interruptions will be presented by treatment group, along with the corresponding reasons.

Prior and Concomitant Treatments

The proportion of patients with prior/concomitant medications will be presented by treatment group using the World Health Organization Drug Dictionary (WHO-DD).

Prior medications will be identified as therapies starting prior to the study and ending prior to randomization (i.e. Day 1). Prior medications will be presented by anatomical therapeutic chemical (ATC) Code Level 2, Preferred Term on the FAS population by study group. Concomitant medications are defined as therapies ending or ongoing after randomization and will be presented, by ATC Code Level 2, Preferred Term and ongoing status on the safety population.

A medication with a missing start date will be assumed to be a concomitant medication unless the stop date is before the randomization date, in which case the medication will be summarized as a prior medication. Medications with start dates before the randomization date and missing end dates will be summarized as concomitant medications.

10.3.4 BASELINE DESCRIPTIVE STATISTICS

All data regarding demographics and baseline characteristics will be summarized on the FAS by means of summary descriptive statistics. A complete description of patient disposition will be provided, specifying the number of randomized patients, discontinued patients, and the reason for the discontinuation.

The analysis populations will be described and the reasons for excluding the patient from any analysis set will be provided with the number of protocol violators per each criterion.

No statistical test will be performed for between-group differences in demographic and baseline characteristics.

Medical history will be described according to System Organ Classes and Preferred Terms using the MedDRA and will be presented by treatment group.

10.3.5 PLANNED INTERIM ANALYSES

No formal interim analysis will be performed.

10.3.6 ANALYSES OF PHARMACODYNAMICS

Descriptive statistics on the Safety population will be presented at baseline and at specified time points for serum TNF-α, IL-1β, IL-6 and CRP levels. If available, the same assessments will be presented for BAL sample results.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1.1 INFORMED CONSENT PROCESS

11.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

11.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be EC/IRB-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and

of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If a patient is incapable of providing consent due to his or her clinical conditions, consent may be obtained from the patient's legal/authorized representative.

In accordance with the European Medicines Agency (EMA) "Guidance on the management of clinical trials during the covid-19 (coronavirus) pandemic version 3 28/04/2020", the following specific aspects of the consent procedure will be taken into account:

- If written consent by the trial participant is not possible (for example because of physical isolation due to COVID-19 infection), consent may be given orally by the trial participant (Art 2(j) of Directive 2001/20/EC) in the presence of an impartial witness. In such cases, the witness is required to sign and date the informed consent form and the investigator is expected to record how the impartial witness was selected.
- In addition, it could be considered that the trial participant and the person obtaining consent sign and date separate informed consent forms.

In either case, all relevant records should be archived in the investigator's site master file. A correctly signed and dated informed consent form should be obtained from the trial participant later, as soon as possible.

11.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform study participants, the EC/IRB, Regulatory Authorities and Sponsor, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, EC/IRB and Regulatory Authorities.

11.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Sponsor. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the EC/IRB and Regulatory Agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing EC/IRB, Institutional policies, Sponsor requirements and local regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the CRO (OPIS s.r.l.) working on behalf of the Sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. Only the study centre will be able to link the study ID number to the patient's identity. The study data entry and study management systems used by clinical sites and by OPIS research staff will be secured and password protected.

11.1.4 FUTURE USE OF STORED SPECIMENS

Not applicable. No biological samples will be stored for future use during this study. Biological samples will be used exclusively for the purposes defined in this protocol.

11.1.5 SAFETY OVERSIGHT

Not applicable.

11.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is compliant with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirements.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information. All information on the eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific Monitoring Plan (MP). No information in source documents about the identity of the patients will be disclosed.

In accordance with the EMA's "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic version 3 28/04/2020", a risk-based approach to monitoring will be implemented focusing on processes that are critical to ensure the rights, safety and well-being of trial participants and the integrity of the trial (and trial data), as well as the extra burden that introduction of these processes may put on site staff and facilities. The MP will be drafted in accordance with these considerations in order to strike an acceptable balance between appropriate oversight and the capacity of the trial site. Critical data for which source data verification (SDV) needs to be performed will be identified in the MP. Results of adjusted monitoring/review measures and their impact will be reported to the sponsor in monitoring reports and in the clinical study report, where applicable. The same guidelines will be implemented in Russia.

Adjusting monitoring activities may include a combination of the following:

a. To the extent on-site monitoring remains feasible, social distancing restrictions, the urgency (e.g. SDV can often be postponed) and the availability of site staff will be taken into account and will only be performed as agreed with trial sites. Additional measures regarding on-site monitoring may include limited, targeted on-site monitoring identifying higher risk clinical sites.
b. Centralised monitoring of data acquired through the eCRF will be implemented to supplement on-site monitoring through a remote evaluation of ongoing and/or cumulative data collected from trial sites in a timely manner.
c. Off-site monitoring activities may include phone calls, video visits, e-mails or other online tools in order to discuss the trial with the investigator and site staff. These activities may be used to acquire information on the clinical trial progress, exchange information on the resolution of problems, review procedures, trial participant status as well as to facilitate investigator training.
d. Remote SDV may be considered since this study involves the treatment of COVID-19 patients. SDV will focus on the quality control of critical data such as primary efficacy data and important safety data. Important secondary efficacy data may be monitored simultaneously, provided this does not result in a need to access additional documents and therefore in an increased burden for trial site staff.

   The data protection officer and principal investigator at each site will be consulted to establish whether remote SDV is allowed, feasible and manageable and what the practicalities may be.

   Site staff will inform each trial participant and ensure that they do not object to the remote review of their records for trial purposes and document this process in the trial participant's medical records. If a trial participant objects to remote review of their records, no remote SDV will occur for that trial participant.

   Performance of remote SDV by the monitor may only occur in locations that prevent viewing by any unauthorised person, through a secure internet connection and on a computer appropriately protected against unauthorised access to the data.

If the agreed remote SDV process involves redaction by the site staff (pseudonymisation) of source records:

- The monitor will provide a written request to the site for the specific participant's specific trial records required for SDV.
- Site staff shall create copies of the requested trial participant's records, redact (i.e. pseudonymise and mask any unnecessary private information unrelated to the trial) the copies, identify them with the trial participant identification code in the trial, have a second person perform and document a quality control to ensure that all identifying information has been redacted and is no longer readable, and make the pseudonymised copies available to the monitor using a secure mechanism. The redacted copies should be kept in the investigator's site master file with records of their communication to the monitor.
- The monitor will access the records securely, complete the monitoring task, securely destroy any copy made locally and provide a certificate of destruction to the trial site.
- Once on-site monitoring visits are again feasible, the monitor should verify at the earliest opportunity that the provided pseudonymised (coded) data are indeed data related to the trial participant with the provided code.

The principal investigators will make their own determination as to whether or not the situation at their clinical site allows any of the following options for remote SDV:

- Sharing pseudonymised copies of trial related source documents with the monitor; this may be done electronically where manageable by the site staff;
- Direct, suitably controlled remote access to trial participants' electronic medical records;
- Video review of medical records with clinical site team support, without sending any copy to the monitor and without the monitor recording images during the review.

These provisions will be in line with the principles of necessity and proportionality and in a way that protects trial participants' rights and will not place any disproportionate burden on site staff as determined by the investigator and trial site staff. Investigators will not be put under undue pressure to accept remote SDV and will always give priority to the care to be given to trial participants and other patients.

11.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Following written Standard Operating Procedures, monitors will verify that the clinical trial is conducted and data generated, documented (recorded), and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

Given the current situation, on-site audits may, in general, be avoided or postponed. Audits should only be conducted if permitted under national, local and/or organisational social distancing restrictions. On-site audits as well as remote audits can be considered, after agreement with the investigator and if the audits are assessed as essential, e.g. triggered audits with the purpose of investigating serious deviations from the trial protocol or from the applicable legislation.

11.1.8 DATA HANDLING AND RECORD KEEPING

11.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the electronic data capture system until they are trained.

Web-based software will be used, and no installation procedure is needed. Each site will be authorized by the administrator to access the eCRF. Each site-qualified personnel will be allowed to access the eCRF by means of a 'login mask' requiring user ID and password and may read, modify, and update only the information entered at his or her site and according to their profile. Each page reports site code and patient code.

On-line validation programs will check for data discrepancies and generate automatic warning messages, allowing the investigator to confirm or correct the data entered. The investigator will certify that the data entered in the eCRF are complete and accurate.

After database lock, the investigator will receive a CD-ROM of patient data for archiving at the investigational site.

Database management and quality control

The CRO working on behalf of the Sponsor will review the data entered in the eCRF by investigational staff for completeness and accuracy and instruct site personnel to make any necessary corrections or additions. The data manager will perform the cleaning session by reviewing the warning messages raised by on-line checks and by running post-entry checks by means of validation programs and data listings specific for the study. The occurrence of any protocol deviations will also be evaluated.

If clarifications are needed, the data manager will raise queries through the web application. Designated investigator site staff will be required to respond to queries and to make the relevant corrections, if needed.

Data collection and query flows, as well as the on-line and off-line checks, are detailed in the Data Management Plan and Data Validation documents.

Concomitant and prior medications entered in the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

The database will be locked after all the above actions have been completed and the database has been declared complete and accurate.

11.1.8.2 STUDY RECORDS RETENTION

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or ICH-GCP. Noncompliance may be on the part of either the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report protocol deviations. All deviations must be addressed in study source documents.

The COVID-19 situation is likely to introduce more protocol deviations than normal. The sponsor will manage such protocol deviations in accordance with standard procedures. The sponsor will perform an analysis of the number and type of deviations periodically to assess whether a protocol amendment or other modifications are needed.

11.1.10 INSURANCE

The Sponsor certifies that it has taken out a liability insurance policy covering this clinical trial. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IRB/EC and/or regulatory authorities.

11.1.11 PUBLICATION AND DATA SHARING POLICY

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor, who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

This study will ensure that the public has access to the published results of the research.

As this is a multicentre study, the first publication must be related to data collected from all patients enrolled and analysed under the Sponsor’s responsibility. The investigator shall not publish or communicate data collected in only one centre or part of the centres before publication of the complete results of the study, unless prior written authorization from the Sponsor has been provided.

Any publication and/or communication project regarding the study and/or its results, whether obtained during the study or after the study end, shall be submitted to the Sponsor at least 30 days for a publication

and 15 days for an abstract before the planned date of communication and/or submission for a publication. The Sponsor shall make comments on the project within 15 days of receipt of the project for a publication and within 7 days for an abstract. The investigator who submitted the project shall take the Sponsor's comments into due consideration. Nevertheless, should the investigator who submitted the project decide not to modify the project according to the Sponsor's comments, he/she shall provide the Sponsor with the grounds for his/her decision in writing.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioural treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies.

11.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11.2 ABBREVIATIONS

ADA	Anti-Drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
Akt	Protein Kinase B
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
aPTT	activated Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	Area Under the Curve
AUC_{inf}	AUC to infinity
AUC_{last}	AUC to Last Quantifiable Concentration
BAL	Bronchoalveolar Lavage
BIPAP	Bilevel Positive Airway Pressure
BUN	Blood Urea Nitrogen
cccDNA	Covalently Closed Circular DNA
CI	Confidence Interval
C_{max}	Maximum Concentration Observed
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease
CPAP	Continuous Positive Airway Pressure
CRO	Contract Research Organization
CRP	C-reactive Protein
CT	Computed Tomography
CUP	Compassionate Use Program
EC	Ethics Committee
EC_{50}	Half maximal effective concentration
eCRF	Electronic Case Report Form
ECMO	Extracorporeal Membrane Oxygenation
EMA	European Medicines Agency
EMC	Encephalomyocarditis
EOT	End of Treatment
FAS	Full Analysis Set
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HED	Human Equivalent Dose
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IFN	Interferon
IL	Interleukin
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRR	Infusion Related Reaction

ITT	Intention to Treat
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
MCP	Monocyte Chemoattractant Protein
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MHV	Mouse Hepatitis Virus
MP	Monitoring Plan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NF-kB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NOAEL	No Observed Adverse Effect Level
OR	Odds Ratio
OS	Overall Survival
PaO_2	Partial Pressure of Arterial Oxygen
PP	Per Protocol
PS	Polysorbates
PT	Prothrombin Time
RRT	Renal Replacement Therapy
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SDV	Source Data Verification
SoA	Schedule of Activities
SOC	Standard of Care
SpO_2	Peripheral Capillary Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to reach maximum concentration
TNF	Tumour Necrosis Factor
TTCI	Time To Clinical Improvement
ULN	Upper Limit of Normal
VSF	Virus Supressing Factor
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WHV	Woodchuck Hepatitis Virus

11.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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