Title: A Phase II Multi-Center, Double-Blind, Randomized and Controlled Study of the Safety and Efficacy of Intravenous Recombinant Human Interferon Beta-1a in Comparison to Dexamethasone for the Treatment of Hospitalized Patients with COVID-19 Infection

NCT number: NCT04860518

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A Phase II Multi-Center, Double-Blind, Randomized and Controlled Study of the Safety and Efficacy of Intravenous Recombinant Human Interferon Beta-1a in Comparison to Dexamethasone for the Treatment of Hospitalized Patients with COVID-19 Infection

HIBISCUS Study Protocol

Human intravenous **I**nterferon **B**eta-**I**a **S**afety and preliminary efficacy in hospitalized subjects with **C**oronavir**US**

Funding/Support:	U.S. Department of Defense and Faron Pharmaceuticals Ltd.
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Interactive Web-Response System (IWRS)	For contact details please refer to the IWRS User Manual in the Investigator Package

SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

A Phase II Multi-Center, Double-Blind, Randomized and Controlled Study of the Safety and Efficacy of Intravenous Recombinant Human Interferon Beta-1a in Comparison to Dexamethasone for the Treatment of Hospitalized Patients with COVID-19 Infection

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 2013, and the ICH guidelines on Good Clinical Practice.

This protocol has been approved by:

Name: [redacted] **Trial Role:** Chief Medical Officer

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Declaration of the Global Co-ordinating Investigator

A Phase II Multi-Center, Double-Blind, Randomized and Controlled Study of the Safety and Efficacy of Intravenous Recombinant Human Interferon Beta-1a in Comparison to Dexamethasone for the Treatment of Hospitalized Patients with COVID-19 Infection

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 2013, and the ICH guidelines on Good Clinical Practice.

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This protocol describes the FP1CLI017 trial and provides information about procedures for trial subjects taking part in the trial. The protocol should not be used as a guide for treatment of patients not taking part in the FP1CLI017 trial.

SUMMARY OF CHANGES

The following changes have been made to this protocol since the first approved protocol version. Changes in more detail can be seen in separate Summary of Changes document(s).

Previous Protocol version and date	Revised Protocol version and date	Description of Change(s)
v1.0, 17Dec2020	v2.0, 05Feb2021	Substantial changes Study treatment in accordance with standard treatment guidelines updated according to FDA recommendations and concomitant baricitinib usage with study IMP prohibited. Systemic baricitinib therapy have been added to the exclusion criteria and exclusion criteria have been further updated to better equate the clinical routine care. MxA, CD73, PIMs (D3), Interferon beta and SARS-CoV-2 sample collection timepoints and the list of PIMs have been updated. Analyses of PIMs and interferon signalling markers using the Nanostring technology has been added. Non-substantial changes Text about oxygen support and mechanical ventilation on Day 28 has been added to the exploratory outcome measures where incoherently described. Age stratification classes specified in the randomization criteria. Table 2 has been updated to be more readable and regarding the chapters 6.2 – 6.5 the chapter order has been rearranged, and text clarified. Also other non-substantial text clarifications and correction of typos have been made through the protocol.
v2.0, 05Feb2021	v3.0, 14Jun2021	The comparator group is changed to dexamethasone and the protocol is updated throughout to match this change. Eligibility criteria updated to exclude patients not requiring supplemental oxygen. Incidence of study treatment discontinuation and transition to an open label corticosteroid is added as exploratory efficacy endpoint. X-ray/CT scans performed as part of standard clinical care are used for COVID-19 diagnostics accuracy, separate X-ray/CT scans are not performed for study purpose. A positive test for COVID-19 must be available for randomization, but now specified that it can be other than a PCR test. Nasal swab sampling and local analysis for viral load is exchanged to serum sampling and analysis at a central laboratory (the maximum additional blood sampling equals 12.5 ml). The AE follow-up period and pregnancy reporting period are further specified.

		Statistical analyses section has been updated with the description of analysing also the use of unblinded corticosteroids as an intercurrent event. Global Co-ordinating investigators is updated with Dr. Ginde, University of Colorado. Also other non-substantial text clarifications and correction of typos have been made throughout the protocol.
v3.0, 14Jun2021	v4.0, 27Sep2021	A baseline nasopharyngeal swab is added for analysis of SARS-CoV-2 variants. All-cause mortality at Days 28 and 90 are added to the secondary endpoints, and efficacy of study treatment based on viral variant and on vaccination status to the exploratory endpoints. The text in inclusion criteria 4 is harmonized with inclusion criteria 3 for better clarity by both referring to respiratory symptoms. Blood sampling for SARS-CoV-2 viral burden is changed from Day 4 to Day 3 to harmonize with other blood sampling. Assessments on subjects that are discharged from the hospital but re-admitted due to COVID-19 have been specified. Description of the study design and risk-benefit assessment are adapted according to FDA's recommendations. Specified that in addition to baricitinib, also concomitant tofacitinib (and other JAK-STAT signalling pathway inhibitors) usage with study IMP is prohibited. Updated that patients who have received at least one dose of study drug will not be replaced for any reasons. Also, other text clarifications and correction of typos have been made through the protocol.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-Drug Antibodies
AE	Adverse Event
AEP	Acute Eosinophilic Pneumonia
AKI	Acute Kidney Injury
ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
BIPAP	Bilevel Positive Airway Pressure
BP	Blood Pressure
CBC	Complete Blood Count
CD73	Cluster of differentiation 73
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
CRA	Clinical Research Associate (Monitor)
CT	Computerised Tomography
D	Day (as in treatment day)
DNR	Do Not Resuscitate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECMO	Extracorporeal membrane oxygenation
e-CRF	Electronic Case Report Form
FAS	Full Analysis Set
FU	Follow-up
HR	Heart Rate
HSP	Hypersensitivity Pneumonitis
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
IRB	Institutional Review Board
IMP	Investigational Medicinal Product

IV	Intravenous
IWRS	Interactive Web-Response System
JAK-STAT	Janus kinase-signal transducer and activator of transcription
MERS	Middle East Respiratory Syndrome
MIU	Million International Units
MOF	Multiple Organ Failure
MM	Medical Monitor
MxA	Myxovirus resistance protein A
NOAEL	No Observed Adverse-Effect Level
OSCI	WHO ordinal scale for clinical improvement
OTD	Optimum Tolerated Dose
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PerLR	Personal Legal Representative
PD	Pharmacodynamics
PIM	Potential Inflammatory Marker
PPS	Per-Protocol Set
PrfLR	Professional Legal Representative
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
WBC	White Blood Cells

1 PROTOCOL SYNOPSIS

Title	**A Phase II Multi-Center, Double-Blind, Randomized and Controlled Study of the Safety and Efficacy of Intravenous Recombinant Human Interferon Beta-1a in Comparison to Dexamethasone for the Treatment of Hospitalized Patients with COVID-19 Infection**
Sponsor Study No.	FP1CLI017
Phase	II
Funding/Support	U.S. Department of Defense and Faron Pharmaceuticals Ltd.
Sponsor	Faron Pharmaceuticals Ltd., Turku, Finland
Co-ordinating Investigators	Professor Daniel Talmor, Harvard Medical School Professor Adit Ginde, University of Colorado School of Medicine
Study Centre(s)	Approximately 5-15 investigational sites located in the USA and possibly also in other countries
Objectives	
Primary Objectives	- To demonstrate the safety and tolerability of early intravenous (IV) IFN beta-1a administration in hospitalized patients with COVID-19 infection compared to dexamethasone - To investigate the efficacy of IV IFN beta-1a to improve clinical status in hospitalized patients with COVID-19 compared to dexamethasone
Secondary Objectives	- To assess the immunogenicity of IFN beta-1a - To investigate the efficacy of IV IFN beta-1a on clinical outcomes in hospitalized patients with COVID-19 compared to dexamethasone
Exploratory Objectives	- To investigate the efficacy of IV IFN beta-1a on additional clinical outcomes in hospitalized patients with COVID-19 compared to dexamethasone - To investigate study treatment discontinuation rate of IFN beta-1a compared to dexamethasone - To investigate the effect of IMPs on viral burden (quantitative) in blood during the disease course - To measure the pharmacodynamic (PD) effects of IFN beta-1a (Myxovirus Resistance Protein A (MxA) and cluster of differentiation 73 (CD73) - To measure IFN beta levels during the treatment - To evaluate potential inflammatory markers (PIMs) and interferon signalling markers at protein and RNA level in response to treatment

- To evaluate genetic susceptibility to IFN beta-1a treatment
- To investigate the efficacy of study treatment based on SARS-CoV-2 variant
- To investigate the efficacy of study treatment based on the vaccination status

Design

This is a multi-center, double-blind, randomized and controlled trial of early IV administration of IFN beta-1a compared with dexamethasone in hospitalized patients with COVID-19 infection not requiring high-flow (> 8L/min) oxygen therapy or mechanical ventilation.

COVID-19 patients in the Emergency Department (ED) or early in hospitalization will undergo screening during which informed consent will be obtained and eligibility assessed by Inclusion and Exclusion criteria. No more than 48 hours may elapse between hospital arrival of the patient and administration of the first dose of the study drug.

At randomization, subjects will be stratified by gender and age to be treated daily either with IV IFN beta-1a 10 µg or IV dexamethasone 6 mg for 6 days while hospitalized and will undergo daily assessments while in hospital for a maximum of 28 days. Study specific assessments will be collected at pre-dose Day 1 through Day 28, in addition, clinical routine assessments will be utilized for safety and efficacy assessments.

Due to preclinical and clinical data demonstrating that concomitant administration of systemic corticosteroids diminishes the effectiveness of IV IFN beta-1a, systemic open-label corticosteroids are not permitted during the 6-day acute intervention period. The requirement for systemic open-label corticosteroid treatment is an exclusion criterion in the study. However, if the Investigator/attending clinician determines that the subject requires open-label corticosteroids during the intervention period (Study Day 1 - Day 6), the investigational medicinal products (IMPs) will be discontinued, and the subject will continue to have the ongoing study assessments. From Day 7 onward corticosteroid treatment will be permitted if required according to the judgment of the treating attending clinician. Same principle should be applied for other co-medications with potential of interacting with IFN beta-1a, such as baricitinib, tofacitinib and other inhibitors of *janus kinase-signal transducer and activator of transcription* (JAK-STAT) signalling pathway.

Specific medical conditions that require immediate corticosteroid treatment are specified in the protocol. Once diagnosed, treatment with IMP should be discontinued and the subjects will continue to have the ongoing study assessments.

Standard treatment practice of COVID-19 should follow treatment guidelines, and should a study patient progress in disease severity requiring increasing amounts of supplemental oxygen, the study medication should be stopped and dexamethasone treatment should

	begin according to guidelines (https://www.covid19treatmentguidelines.nih.gov/therapeutic-management). Remdesivir does not impact study treatment. The main analysis and reporting will use Day 28 data after the last study subject has completed the Day 28 assessments. An Independent Data Monitoring Committee (IDMC) will be established to monitor safety on an ongoing basis.
Study treatments	Investigational medicinal products (IMPs): - IFN beta-1a 10 µg (recombinant human IFN beta-1a) or Dexamethasone 6 mg will be administered once daily as an IV bolus injection for 6 days. - To maintain blinding at administration, every study subject will receive two separate bolus injections of IMP (either IFN-beta -1a/saline, and another injection of Saline/Dexamethasone). Study IMPs will be prepared by an unblinded person according to the randomization code.
Number of Study subjects	140 subjects with COVID-19 infection will be randomized at approximately 5-15 investigational sites.
Population	The inclusion and exclusion criteria apply during screening and prior to administration of the first dose of study drug on Day 1.
Inclusion Criteria	1. Age ≥18 years 2. Positive SARS-CoV-2 test by PCR (polymerase chain reaction) or other diagnostic method within the past 7 days 3. Admission to hospital with respiratory symptoms of COVID-19 requiring hospital care and oxygen supplementation (≤ 8L/min) 4. Respiratory symptom onset no more than 7 days prior to hospital arrival 5. Informed consent from the subject or the subject's personal legal representative or a professional legal representative must be available
Exclusion Criteria	1. Unable to screen, randomize and administer study drug within 48 hours from arrival to hospital 2. Systemic corticosteroid, baricitinib, tofacitinib or other JAK-STAT signalling pathway inhibiting therapy within 7 days prior to arrival to hospital or planned for the next days 3. Known hypersensitivity or contraindication to natural or recombinant IFN-beta-1a or its excipients, or to dexamethasone or its excipients 4. Currently receiving IFN-beta-1a therapy 5. Home assisted ventilation (via tracheotomy or non-invasive) except for Continuous Positive Airway Pressure (CPAP) / Bilevel

Positive Airway Pressure (BIPAP) used only for sleep-disordered breathing

6. Participation in another concurrent interventional pharmacotherapy trial during the study period
7. Decision to withhold life-sustaining treatment; patient not committed to full support (except DNR after cardiac arrest only)
8. Woman known to be pregnant, lactating or with a positive pregnancy test (urine or serum test)
9. Subject is not expected to survive for 24 hours
10. Subject has liver failure (Child–Pugh grade C)
11. Any clinical condition that in the opinion of the attending clinician or Investigator would present a risk for the subject to participate in the study

Criteria for Evaluation of Safety

- Adverse events, serious adverse events, and deaths
- Physical examination, vital signs and laboratory results (biochemistry, haematology) collected as standard of care routine
- Immunogenicity as measured by anti-IFN beta antibodies

Criteria for Evaluation of Efficacy

Primary Efficacy Endpoint:

- Clinical status at Day 14 (first day of study drug is Day 1) as measured by WHO 9-point ordinal scale:
  0 - No detectable infection
  1 - Not hospitalized, no limitations on activities
  2 - Not hospitalized, limitation on activities
  3 - Hospitalized, not requiring supplemental oxygen
  4 - Hospitalized, requiring supplemental oxygen
  5 - Hospitalized, on non-invasive ventilation or high flow oxygen devices
  6 - Hospitalized, on invasive mechanical ventilation
  7 - Hospitalized, on mechanical ventilation plus additional organ support: renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO)
  8 - Death

Secondary Efficacy Endpoints:

- Clinical status at Day 28 as measured by WHO 9-point ordinal scale
- In-hospital mortality at Day 28 and Day 90
- Overall (all-cause) mortality at Day 28 and Day 90

Criteria for Evaluation of Exploratory Endpoints

Exploratory Efficacy Endpoints

- Incidence of Acute Respiratory Distress Syndrome (ARDS)
- Incidence of Acute Kidney Injury (AKI)
- Incidence of new mechanical ventilation

- Days alive and free of renal support at Day 28
- Days alive and free of ECMO at Day 28
- Days alive and free of oxygen support at Day 28
- ICU-days at Day 28
- Days on mechanical ventilation on Day 28
- Length of Hospital stay among survivors at Day 90
- Incidence of study treatment discontinuation and transition to an open label corticosteroid
- Association of the efficacy outcome measures of study treatment with vaccination status

Exploratory Laboratory Efficacy Endpoints

- Quantitative PCR for SARS-CoV-2 in blood on pre-dose Day 1 and Day 4, Day 7, Day 10 and on Day 14 (only for hospitalized patients, if patient's discharge is before D14, the specimen is obtained also on the day of discharge)
- CD73 in blood on pre-dose Days 1, 3, 5 and on Day 7 (only for hospitalized patients)
- INF beta levels in blood on Day 1 pre-dose, Day 1 (5 minutes after dosing), pre-dose on Day 3 and on Day 7 (only for hospitalized patients)
- Association of baseline IFN-beta level (possible deficiency in endogenous IFN-beta response to viral infection) with the disease outcome (WHO 9-point ordinal scale)
- MxA levels in blood on pre-dose Days 1, 3, 5 and on Day 7 (only for hospitalized patients)
- Changes in levels of potential inflammatory markers (PIMs) at protein and RNA level on pre-dose Days 1, 3, 5 and on Day 7 (only for hospitalized patients)
- Correlation of pharmacogenetic markers with PD markers of IFN beta-1a activity, and disease outcome measures
- Association of the efficacy outcome measures of study treatment with the variant of SARS-CoV-2 and vaccination status

Statistical Methods

Statistical power and sample size justification:

140 patients will be randomised 1:1 for active: comparator. Conditional power re-assessment will be conducted at an interim analysis after circa 70 patients have been enrolled and followed up for the primary efficacy endpoint variable. The primary variable is the clinical status at Day 14 using a WHO 9-point scale (0=no detectable infection to 8=death). It will be analysed using ordinal logistic regression model comparing the odds of having better clinical status (smaller number in the 9-point scale) at day 14 between treatment groups. The sample size is based on

an assumption of odds ratio of 0.43 between groups leading to a power of 80% with 70 evaluable patients per group. In the interim analysis the conditional power will be calculated based on the observed result and the sample size will be increased in case the conditional power is in the predefined promising zone. Futility analysis is not included at interim.

Dichotomous secondary efficacy variables will be analysed using logistic regression models and time-to-event variables using Cox proportional hazards models. Other secondary variables with non-gaussian data (e.g., variables measuring number of days) will be analysed using general linear models or non-parametric methods

Analysis Sets:

The Full Analysis Set (FAS) will consist of all randomized patients who receive at least one dose of study medication.

The Per-Protocol Set (PPS) will consist of those subjects in the FAS excluding subjects with major protocol violations.

A list of major protocol violations relevant for excluding data from the PPS will be detailed in the Statistical Analysis Plan. The precise definition of the PPS at the subject level will be identified at the blinded data review meeting before the interim and final analysis.

Statistical analyses for the primary and secondary endpoints will be performed on both the FAS and PPS.

The safety set will consist of all subjects who receive at least one dose of the study IMPs. The safety and tolerability analyses will be based on this analysis set. A subject who receives the wrong treatment according to the randomization will be analysed for safety and tolerability in the treatment group corresponding to the treatment received.

2 INTRODUCTION

This is a Phase II clinical study to investigate the safety and efficacy of intravenous (IV) recombinant human interferon (IFN) beta-1a in hospitalized patients with COVID-19 infection not requiring high-flow oxygen or mechanical ventilation. The study was initially planned to compare active drug to placebo, but compliance with treatment guidelines for patients with supplemental oxygen prompted a change in the comparator arm to dexamethasone instead of placebo. Recombinant human IFN beta-1a is an approved treatment as an intramuscular (IM) or subcutaneous (SC) formulation for subjects with multiple sclerosis and its safety profile in these subjects is well characterised. IV IFN beta-1a has been administered previously to 314 critically ill patients in phase I-III clinical studies for the treatment and prevention of Multiple Organ Failure (MOF) and Acute Respiratory Distress Syndrome (ARDS) (The ARDS Definition Task Force 2012). Tolerability has been good in critically ill patients (Ranieri et. al. 2020), and in healthy volunteers (FP1CLI011 clinical study report). IFN beta-1a should not be administered with concomitant systemic corticosteroids, as corticosteroids may inhibit IFN beta signalling (Jalkanen et al. 2020) and may impair the up-regulation of CD73 (Kiss et. al. 2007) on vascular endothelium. Administering IFN beta-1a IV achieves broader exposure in the circulation, compared to SC or IM routes of administration (Buchwalder et. al. 2000). Therefore, IV administration is a desired administration method to achieve efficient CD73 upregulation and effect on vascular integrity, especially in pulmonary circulation and under critical illness conditions.

2.1 Background on COVID-19

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infectious illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Del Rio and Malani 2020 and Fauci et al. 2020). The COVID-19 infection represents the seventh coronavirus known to cause disease in humans. (Li et al. 2020). Four of the coronaviruses are known to cause symptoms of the common cold in immunocompetent individuals while two others (SARS-CoV and MERS-CoV) have caused recent outbreaks of severe and sometimes fatal respiratory diseases (Cui et al. 2019). SARS-CoV-2 appears to exploit the same cellular receptor as SARS-CoV and MERS-CoV, and thus the effects of IFN beta on SARS-CoV2 are likely to be very similar to these prior coronaviruses (Zhou et al. 2020).

Although the epidemiology has not been fully elucidated, many adults with COVID-19 appear to experience fever, cough, and fatigue and then recover within 1-3 weeks. However, approximate 20% of adults with COVID-19 develop severe illness, typically manifesting as pneumonia and acute hypoxemic respiratory failure, with continued progression to ARDS and death in some cases (Del Rio and Malani 2020, Fauci et al. 2020, Li et al. 2020).

ARDS is a type of acute lung injury characterized by dysregulated inflammation, coagulopathy, and accumulation of immune cells, leading to injury of the endothelial barrier, increased permeability of the alveolar-capillary barrier, and non-cardiogenic pulmonary edema. Although mortality from ARDS appears to have decreased in the last couple of decades due to improvements in supportive care including lung protective ventilation and in the treatment of underlying conditions, it still remains up to 40% in moderate or severe ARDS. In addition, the impairment to quality of life among ARDS survivors is significant. At two years after a diagnosis of moderate to severe ARDS, approximately 35% of patients are still unable to return to work (Kamdar et al. 2018). There are currently no approved pharmacological therapies for ARDS.

2.2 Scientific justification for IFN beta-1a for COVID-19

2.2.1 IFN beta and Severe Coronavirus disease

IFN beta is a type I IFN, an endogenous signalling protein made and released by host cells in response to the presence of a viral infection. It is a natural defence mechanism released by virus infected cells to enhance the resistance of uninfected cells. Type I IFN deficiency has been associated with severe COVID-19 disease previously (Hadjadj et al. 2020, Zhang et al. 2020).

Prior data indicates that treatment with IFN beta enhances viral clearance and improves clinical outcomes for Middle East Respiratory Syndrome (MERS) coronavirus in nonhuman primates (Chan 2015). In addition, IFN alpha-2b combined with ribavirin reduced viral replication, moderates host response, and improves clinical outcomes in nonhuman primates with MERS coronavirus (Falzarano 2013). In addition, a retrospective study of IFN alpha-2a combined with ribavirin was associated with lower mortality in MERS coronavirus (Omrani 2014). Recently, a clinical study by Arabi et al. (2020) showed that IFN beta significantly reduced mortality in MERS if given within 7 days of symptom onset. Concerning COVID-19, *in vitro* studies have shown that IFN beta inhibits replication of SARS-CoV-2 (Lokugamage et al. 2020) and has shown effect in treating hospitalized COVID-19 patients both in IM (Hung et al. 2020) or inhaled form (Monk et al. 2020).

The effect of IFN beta on COVID-19 was investigated in SOLIDARITY (WHO Solidarity Trial Consortium 2021) and ACTT-3 (NCT04492475) trials. In both trials overlapping use of corticosteroids with IFN beta-1a was permitted. In SOLIDARITY, approximately half the patients who were assigned to IFN beta (and half their controls) received concomitant glucocorticoids. Same information is not available for the ACTT-3 trial. Therefore, potential beneficial effects of IFN beta-1a may have been mitigated by the concomitant use of corticosteroids in these trials. In these previous trials IFN beta-1a was almost entirely used in its subcutaneous form, which does not deliver the drug to the lung endothelium.

2.3 IV IFN beta-1a

IV IFN beta-1a has originally been developed for the prevention and treatment of cytokine release and capillary leak, based on CD73 induction. The first human studies have been conducted in acute lung injury (ALI) (Bellingan et al. 2014) and in ARDS (Ranieri et al. 2020). In serious life-threatening situations, such as infection leading to sepsis or ARDS, an escalation of the systemic inflammatory response leads to ARDS and MOF. In the case of respiratory failure and ARDS, a key pathophysiological result is increased vascular leakage, which has been suggested to be related to a lack of adenosine, which acts to enhance endothelial barrier function. Therefore, any biological substances that act to increase adenosine levels should reduce vascular leakage and be of benefit in ARDS. Such a substance is cluster of differentiation 73 (CD73) – a cell surface enzyme. Interferons, such as IFN beta-1a, have been shown to up-regulate CD73 and therefore could be a potential treatment for ARDS. Preclinical studies have shown that CD73 expression on endothelial cells is up-regulated by IFN beta-1a treatment in a time- and dose-dependent fashion. (Kiss et al. 2007) Furthermore, in a mouse multi-organ failure model, IFN beta was shown to be of benefit in protecting the alveolar structure from damage compared with controls (Kiss et al. 2007). In addition, IFN beta treatment has been shown to prevent leakage in animal models of ALI (Kiss et al. 2007). Enhanced adenosine production also controls leukocyte infiltration, thus reducing the escalation of inflammation in lungs.

2.3.1 Toxicological studies

A 28-day safety study was conducted in cynomolgus monkeys at three IV dose levels 0.25, 1.0 and 3.0 million international units (MIU)/kg/d, which were well tolerated. IFN beta-1a -treatment was associated with minor changes in haematological and clinical chemistry variables, including an expected increase in concentrations of MxA in the blood and increased neutralising antibody activity on completion of treatment, particularly at the highest dose. The no observed adverse-effect level (NOAEL) for IFN beta-1a was considered 3.0 MIU/kg/d for 28 days. In a 70 kg human this would translate to a dose of 210 MIU/d or a total dose of 1260 MIU over 6 days. The proposed daily dose for this clinical study is 2.7 MIU/d (10 µg/d), i.e., a total of 16.2 MIU (60 µg) over 6 days. The NOAEL is therefore 77.7 times the proposed 6-day exposure to IFN beta-1a.

2.3.2 Phase II dose finding study

Recombinant human IFN beta-1a (FP-1201; a liquid formulation / drug product) was assessed for the treatment of ALI and ARDS (1994 American-European Consensus Conference definition of ALI/ARDS (Bernard et al 1994)) in a Phase I/II study (FPCLI001, clinicaltrials.gov: NCT00789685) (Bellingan et al 2014). This open-label study included 37 subjects with ALI/ARDS and the optimum tolerated dose (OTD) for IFN beta-1a (FP-1201) was shown to be 10 µg daily for 6 days. The primary efficacy endpoint was the Day 28 mortality rate, which was 8.1% in the safety population. From the literature, Day 28 mortality rates for ALI/ARDS vary from 20% (ALI) to over 60% (ARDS), with a generally accepted figure of approximately 40%. (Phua et. al. 2009, Doyle et. al. 1995, Zilberberg et. al. 1998, Sloane et. al. 1992) The long-term efficacy endpoint of 6-month mortality also demonstrated a mortality rate well below that expected for this population of patients. Only four of the 37 subjects died before the 6-month time point.

2.3.3 Phase III studies INTEREST and MR11A8-2

A phase III clinical trial (FPCLI002, clinicaltrials.gov: NCT02622724) (Bellingan et. al. 2017) was recently completed. The use of 10 µg daily dose of lyophilized IFN beta-1a (FP-1201-lyo) for six days was not associated with reduced mortality or ventilator use. D28 mortality in the FP-1201-lyo group was 26% and in the placebo group 23%. Post hoc analyses of the FPCLI002 study indicates that glucocorticoid use was significantly associated with an increased risk of mortality in this study population even when taking into account disease severity. Subjects receiving FP-1201-lyo without concomitant glucocorticoids had D28 mortality of 11% compared with 32% mortality in subjects receiving concomitant glucocorticoids. Additional *in vitro* and *ex vivo* analyses of human lung tissue demonstrated that glucocorticoids inhibit the effect of IFN beta-1a to up-regulate CD73 on lung capillary endothelium. In addition, a genetic polymorphism located in a regulatory motif of the IFN alpha/beta receptor beta chain gene (the polymorphic site is a binding site for glucocorticoid receptor) was found to be associated with lower mortality (D28 mortality 11 % regardless of glucocorticoids use). This indicates that without the interfering effect of glucocorticoids on CD73 induction, FP-1201-lyo may reduce mortality.

A Japanese phase III trial (MR11A8-2) was also recently completed. The trial closed recruitment early after an interim analysis triggered by the European Phase III results and Independent Data Monitoring Committee's recommendation. The trial enrolled a total of 87 subjects (45 subjects in FP-1201-lyo and 42 in placebo groups). D28 mortality in the FP-1201-lyo group was 40% and in the placebo group 21%. The use of corticosteroids was even higher being 77%, compared to that of the INTEREST trial. In post hoc analyses, subjects receiving FP-1201-lyo without overlapping glucocorticoids had D28 mortality of 23 % compared with 47 % mortality in subjects receiving overlapping glucocorticoids.

2.3.4 Clinical safety experience of IV IFN beta-1a

In all of the above-mentioned trials, the use of IFN beta-1a has not been associated with significantly increased risks or adverse events in comparison to placebo. Fever was the most common adverse event in both phase III trials.

In the INTEREST trial, 18 (12.5%) study subjects and 12 (7.9%) study subjects in the IFN beta-1a group and placebo groups, experienced fever as an AE. Anaemia was the second most common AE (16 [11.1%] study subjects and 11 [7.2%] study subjects in the IFN beta-1a group and placebo groups, respectively).

In the Japanese phase III trial (MR11A8-2) fever was reported more frequently (34.7% and 6.8%) as an AE for IFN beta-1a and placebo groups, respectively. The second most commonly reported AE was decreased platelet count (6.1%) in the IFN beta-1a group and increased hepatic enzymes (6.8% in both groups).

The incidence of serious adverse events (SAEs) in the INTEREST trial (fatal and non-fatal) was similar in the active (53.5%) and placebo (50.7%) groups. The overall incidence of AEs considered related to study drug was higher in the active group (28.5%) compared with the placebo group (21.7%).

The incidence of SAEs in the MR11A8-2 trial (fatal and non-fatal) was similar in the active (53.1%) and placebo (47.7%) groups, but none of the events were strongly suspected of being causally related to the study drug.

In healthy volunteers IV IFN beta-1a induced a decrease in circulating neutrophils below lower limit of normal approximately three days after the first dose. Blood neutrophils returned to normal range within a few days after the last administered dose. One possible explanatory mechanism is that IFN causes the transfer of neutrophiles from the blood to the tissue (“marginalization) as a precaution to IFN signal and against the possibility of viral presence. In severely ill patients in clinical studies FPCLI002 and MR11A8-2 a similar phenomenon was not observed (Clinical study FP1CLI011, Faron data on file).

2.4 Dexamethasone

2.4.1 Clinical safety experience of Dexamethasone

I.V dexamethasone is recommended therapy for hospitalized patients with hypoxemia who are receiving oxygen through a high-flow device, or non-invasive ventilation, or invasive ventilation. It is also recommended for patients receiving increasing amounts of supplemental oxygen therapy (https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/corticosteroids/). It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate the deleterious systemic inflammatory effects in patients with severe form of COVID-19.

The incidence of side effects associated with the use of dexamethasone generally correlates with dosage, timing of administration, and duration of treatment. The most commonly occurring side effects of dexamethasone have included a wide range of psychiatric reactions, psychotic reactions, behavioural disturbances, irritability, anxiety, sleep disturbances and cognitive dysfunction including confusion and amnesia, decreased blood eosinophils and lymphocytes, increased infection susceptibility, masking of infection signs, aggravated infection, and fungal infections of mucous membranes and the skin. In adults the frequency of severe reactions has been estimated to be 5-6%.

In this study, 6 mg IV doses of dexamethasone will be administered for 6 days. Adverse reactions associated with the use of glucocorticoids are usually dependent on the dose and the duration of the

treatment. Treatment duration of 6 days is relatively short, and the occurrence of the above-mentioned reactions associated with long-term use is unlikely.

2.5 Potential Interaction of glucocorticoids with IFN beta

The results of the Phase I/II study (FPCLI001) and Phase III studies (FPCLI002 and MR11A8-2) provided evidence for the beneficial effect of intravenously administered IFN beta-1a in study subjects with ARDS and also potentially significant interaction caused by concomitantly used corticosteroids. Therefore, a new controlled Phase II study should not allow the overlapping use of glucocorticoids with IFN beta-1a treatment.

The dose selected for this study (10 µg) is based on information from the previous studies, where the maximum tolerated dose was found to be 22 µg. A dose of 10 µg was shown to be the OTD based on information from dose-limiting toxicity and proven markers of IFN beta-1a biological activity. An expansion cohort of 22 subjects treated with the OTD (10 µg) demonstrated preliminary evidence for the efficacy and biological activity of IFN beta-1a using proven surrogate markers without major safety concerns and in the previous Phase III Study (INTEREST) 10 µg dose of IFN beta-1a was proven safe and indicative of efficacy if not used together with glucocorticoids. Banning the use of glucocorticoids during the use of IFN beta-1a is rational, since glucocorticoids have not shown any benefit in early or mild COVID-19. On the contrary, in early COVID-19 and viral induced ARDS (the treatment window for IFN beta-1a) glucocorticoids have instead shown more harm than good (Hough 2014, Zhang et al. 2015, The RECOVERY Collaborative Group 2020). The only possible beneficial effect of glucocorticoids has been shown in more severe COVID-19 patients that require supplemental oxygen or mechanical ventilation.

In this study, standard treatment should follow treatment guidelines, and should a study patient progress in disease severity requiring increasing amounts of supplemental oxygen, the study medication should be stopped and dexamethasone treatment should begin according to guidelines (https://www.covid19treatmentguidelines.nih.gov/therapeutic-management). Remdesivir treatment should also be applied according to the treatment guidelines and standard of care for every subject without contraindication (remdesivir does not impact study treatment).

Additionally, specific corticosteroid responsive conditions (Table 1) should be treated adequately, and if diagnosed during the administration of the study drug (IFN beta-1a/dexamethasone), proper treatment with corticosteroids should not be delayed, but the study drug should be immediately discontinued, for the safety interest of the study subjects. Such patients will be followed according to the protocol and included in the intent-to-treat analysis. Patients may receive open-label antivirals, or immunomodulators (other than glucocorticoids) and remain in the study without discontinuing study drug. Use of such interventions will be reported and analyzed.

Table 1. Specific conditions necessitating corticosteroid treatment and discontinuation of the IFN beta-1a treatment

Condition
Acute eosinophilic pneumonia (AEP)
Diffuse alveolar hemorrage from vasculitis
Crytogenic organizing pneumonia
Acute hypersensitivity pneumonitis (HSP)
Pneumocystis jiroveci pneumonia complicating human immunodeficiency virus (HIV)
Nonspecific interstitial pneumonitis and pneumonitis associated with connective tissue disease

2.6 Risk/Benefit Assessment and Summary of Rationale

COVID-19 pandemic is a major health concern with insufficient effective treatment options. IFN beta represents a naturally occurring viral defence, but if deficient, associated with more severe disease outcome (Hadjadj et al. 2020, Zhang et al. 2020). ARDS is a severe condition with a high mortality rate, despite progress in ICU medicine. Currently there is no approved pharmacological therapy available for ARDS. Patients with ARDS are treated with intensive support, which includes various strategies for assisted ventilation. Therefore, IV IFN beta-1a is a plausible treatment option to be investigated for the treatment of hospitalized COVID-19 and prevention of the development of ARDS. This is what the current study aims to achieve.

The previous results of the Phase I/II and Phase III studies in ARDS provided evidence for the beneficial effect of IFN beta-1a if not used together with corticosteroids. The safety profile of IFN beta-1a does not indicate serious adverse events based on one phase I study in healthy volunteers and two phase III studies in subjects with ARDS. Observed finding of neutrophils marginalization only in healthy volunteers (although not in severely ill ARDS patients), warrants investigation of complete blood count and leukocyte differential to monitor blood neutrophil levels in this study also.

Non-clinical data from conventional studies of safety, pharmacology, repeated-dose toxicity and genotoxicity reveal no special hazard for humans treated with IFN beta-1a.

Phase III clinical studies (INTEREST and MR11A8-2) and phase I clinical study (FP1CLI011) in healthy volunteers did not identify any major safety risks for FP-1201-lyo. A decrease in IL-6 IL-8 and IFN-gamma values was observed in patients treated with FP-1201-lyo, a finding that was similar to those found in a placebo group (Ranieri et al. 2020). Fever was the most common AE in phase III studies, and all healthy volunteers in the study FP1CLI011 experienced fever as a response to the treatment. The pyrogenic effect is characteristic for IFN beta-1a as well as for other type I IFNs. In healthy volunteers, the body temperature characteristically reached 38–39°C (axillary) 1-2 hours after the FP-1201-lyo administration, and this elevation persisted for around 2 hours (all treated with antipyretic analgesics). The temperature elevations vary substantially among individuals. IFN beta-1a induced fever responds to antipyretic analgesic drugs, which are recommended to decrease (or prevent) the flu-like symptoms associated with IFN beta-1a administration. Serious adverse reactions possibly related to IFN beta-1a reported more than once in phase III clinical trials, include two cases of increased transaminases, two cases of thrombocytopenia, three cases of hypertension, and two cases of rhabdomyolysis. The available information suggests that the present study's risk/benefit ratio is favourable.

Investigating the effect of IFN beta-1a to prevent ARDS in viral pneumonia (and particularly SARS-CoV-2) is especially intriguing because of the potential beneficial effects of IFN beta-1a in direct viral defense, association of type I IFN deficiency with worse outcomes in COVID-19 (Hadjadj et al 2020, Zhang et al. 2020), and the induction of CD73-mediated preventive effects on endothelial barrier function and pulmonary capillary leak. The current study aims to detect the benefit of IFN beta-1a in clinical outcome measures (WHO 9-point ordinal scale), reduced need of mechanical ventilation, mortality and development of organ failure and ARDS versus the current standard of care for COVID-19. Dexamethasone was chosen as the comparator arm to align with treatment guidelines for hospitalized COVID-19 patients requiring supplemental oxygen. The rationale underlying the current design is provided below. Safety of both treatment arms will be assessed equally.

Study subjects will be randomized in a 1:1 ratio of IFN beta-1a: dexamethasone. According to current NIH COVID-19 treatment guidelines, dexamethasone can be considered for all patients receiving increasing amounts of supplemental oxygen, but remdesivir without dexamethasone is a reasonable

treatment option for patients requiring minimal levels of supplemental oxygen. Remdesivir does not impact study treatment.

In the current study, the target population is mild COVID-19 subjects with a need for low levels of supplemental oxygen. Subjects randomised to IFN beta-1a treatment will not receive dexamethasone while on IFN beta-1a, but will receive it if deterioration occurs, at which point IFN beta-1a will be discontinued. However, not receiving dexamethasone should not subject the study participants to an increased risk for harm for the following reasons:

In the RECOVERY trial (on which the NIH recommendations are largely based), increasing benefit from corticosteroids was associated with increased COVID-19 severity. The greatest benefit was seen in patients receiving invasive mechanical ventilation, somewhat less benefit in patients receiving supplemental oxygen (but not invasively ventilated), and no benefit – with a suggestion of harm - in patients not receiving supplemental oxygen (The RECOVERY Collaborative Group 2020). Unfortunately, the RECOVERY trial data were not sufficiently granular to identify the impact of the dose of oxygen in non-intubated patients, i.e., supplemental oxygen at low flows vs higher flow conventional oxygen vs high flow nasal oxygen vs non-invasive ventilation. Nonetheless, these data suggest a dose-response curve for benefit in relation to the patient's underlying severity of disease, as determined by the application of supplemental oxygen. Given this dose-response, it is uncertain if subjects with low flow supplemental oxygen derive any benefit from dexamethasone.

The rationale to randomise patients (IFN beta-1a or dexamethasone) with hospitalized COVID-19 patients requiring lower flow oxygen supplementation is justified; IFN beta is an anti-viral that should be initiated relatively early for COVID-19 to enhance the dual mechanisms: natural anti-viral effect + protection of alveolar-capillary barrier function (see Sections 2.2.1 and 2.3). Corticosteroids are very effective immunosuppressants, but strong immune-suppression early in the disease course may be detrimental as evidenced by data suggesting worse outcomes with dexamethasone in COVID-19 patients with mild disease, i.e., those hospitalized patients not receiving supplemental oxygen. Study subjects randomised to IFN beta-1a, will not receive dexamethasone at the earliest stage of the disease (while on low flow supplemental oxygen), but importantly, will receive it should their condition deteriorate as evidenced by the need for higher doses of supplemental oxygen (i.e., high flow oxygen at flow rates greater than 10 l/min, use of high flow nasal oxygen, non-invasive ventilation, or invasive ventilation).

3 STUDY OBJECTIVES

3.1 Primary Objective

- To demonstrate the safety and tolerability of early IV IFN beta-1a administration in hospitalized patients with COVID-19 infection compared to dexamethasone
- To investigate the efficacy of IV IFN beta-1a to improve clinical status in hospitalized patients with COVID-19 compared to dexamethasone

3.2 Secondary Objectives

- To assess the immunogenicity of IFN beta-1a
- To investigate the efficacy of IV IFN beta-1a on clinical outcomes in hospitalized patients with COVID-19 compared to dexamethasone

3.3 Exploratory Objectives

- To investigate the efficacy of IV IFN beta-1a on clinical outcomes in hospitalized patients with COVID-19 compared to dexamethasone
- To measure the pharmacodynamic (PD) effects of IFN beta-1a (MxA and CD73)
- To measure IFN beta levels during the treatment
- To evaluate potential inflammatory markers (PIMs) and interferon signalling markers at protein and RNA level in response to treatment
- To evaluate genetic susceptibility to IFN beta-1a treatment
- To investigate study treatment discontinuation rate of IFN beta-1a compared to dexamethasone
- To investigate the effect of IMPs on viral burden (quantitative) in blood during the disease course
- To investigate the efficacy of study treatment based on SARS-CoV-2 variant
- To investigate the efficacy of study treatment based on the vaccination status

3.4 Outcome Measures

3.4.1 Primary outcome measure

- Clinical status at Day 14 (where first day of study drug is Day 1) as measured by WHO 9-point ordinal scale:
    0. No detectable infection;
    1. Not hospitalized, no limitations on activities;
    2. Not hospitalized, limitation on activities;
    3. Hospitalized, not requiring supplemental oxygen;
    4. Hospitalized, requiring supplemental oxygen;
    5. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
    6. Hospitalized, on invasive mechanical ventilation;
    7. Hospitalized, on mechanical ventilation plus organ support: RRT or ECMO;
    8. Death.

3.4.2 Secondary outcome measures

- Clinical status at Day 28 as measured by WHO 9-point ordinal scale:
    0. No detectable infection;
    1. Not hospitalized, no limitations on activities;
    2. Not hospitalized, limitation on activities;
    3. Hospitalized, not requiring supplemental oxygen;
    4. Hospitalized, requiring supplemental oxygen;

5. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
6. Hospitalized, on invasive mechanical ventilation;
7. Hospitalized, on mechanical ventilation plus organ support: RRT or ECMO;
8. Death.

- Outcome measures relating to the efficacy of IFN beta-1a treatment:
  - In-hospital mortality at Day 28 and Day 90
  - Overall (all-cause) mortality at Day 28 and Day 90

3.4.3 Exploratory outcome measures

- Incidence of ARDS
- Incidence of Acute Kidney Injury (AKI)
- Incidence of new mechanical ventilation
- Days alive and free of renal support at Day 28
- Days alive and free of ECMO at Day 28
- Days alive and free of oxygen support, Day 28
- ICU-days at Day 28
- Days on mechanical ventilation on Day 28
- Length of Hospital stay among survivors at Day 90
- Incidence of study treatment discontinuation and transition to an open label corticosteroid
- PD markers (CD73 and MxA) possibly related to the natural IFN responses, as well as to the IFN beta-1a treatment
- Potential inflammatory and interferon signalling (e.g., IL-6, IL-8) markers at a protein and RNA level (Nanostring) in response to treatment.
- Quantitative analysis (PCR) for SARS-CoV-2 from serum samples.
- Genetic susceptibility to IFN beta-1a treatment, including but not limited to, by screening for SNP rs9984273 and surrounding area which is the glucocorticoid regulatory motif area of IFN alpha/beta receptor subunit 2 (IFNAR2)
- Association of the efficacy outcome measures of study treatment with the variant of SARS-CoV-2
- Association of the efficacy outcome measures of study treatment with the vaccination status

4 OVERALL DESIGN AND PLAN OF THE STUDY

4.1 Overview

This is a multicentre Phase II, double-blind, randomized and controlled, study of the safety and preliminary efficacy of IV IFN beta-1a compared with dexamethasone in adult patients diagnosed with COVID-19 needing hospitalization, but not invasive mechanical ventilation or high flow/pressurized supplemental oxygen. The primary endpoint safety and tolerability of IV IFN beta-

1a, and primary efficacy endpoint is WHO ordinal scale for clinical improvement (WHO OSCI) score at D14. Both treatment groups will receive standard care according to current treatment guidelines, except open-label corticosteroids during study days D1-D6 (or other co-medication with potential of interacting with IFN beta-1a; Section 5.7). If the patient receives (oral or intravenous) glucocorticoids during study days D1-D6, the IMP will be discontinued, and the patient will continue with in all follow-up study assessments.

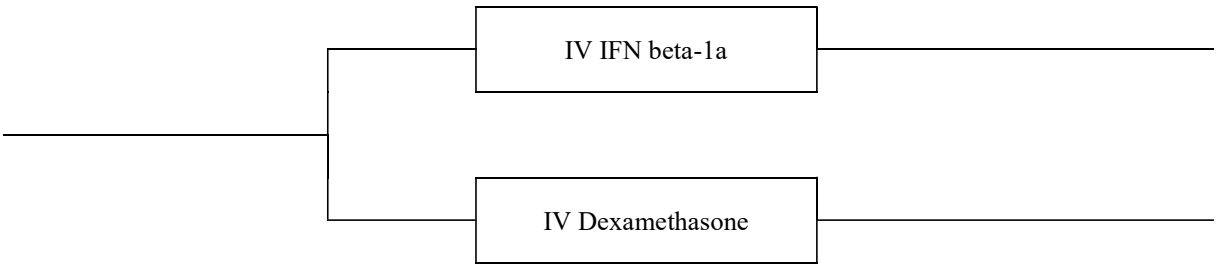
Approximately 140 subjects are planned. Patients with COVID-19 admitted to hospital will undergo screening during which written informed consent will be obtained and eligibility assessed. Not more than 48 hours may elapse between arrival to hospital and administration of the first dose of study drug. An interactive web-response system (IWRS) will be used to randomise the patients using age and gender as stratification parameters.

Following randomization, patients will be treated daily with IFN beta-1a 10 µg or dexamethasone 6 mg as an IV bolus for 6 days and will undergo daily assessments while hospitalized. The main analysis and reporting will use D14 and D28 data. D90 data will be analysed separately. Final follow-up will occur at D90 by phone or through medical records. The overall duration of the study for a patient is therefore 3 months. During the long-term follow-up periods patient care will follow normal hospital procedures, as appropriate. The study will be completed when the last patient completes D90 study assessment. The study design is summarised in Figure 1.

Discontinuation criteria for individual patients and the entire study are described in Section 4.8.1.

The study design incorporates an Independent Data Monitoring Committee (IDMC) that will review ongoing safety (i.e., adverse events [AEs] and serious AEs [SAEs]) and will also make recommendations to the Sponsor as described in the IDMC charter. Details of the IDMC are given in Section 8.8.

A schedule for the tests and assessments to be conducted during this study is given in Section 6 (Table 2).



Day	D1 pre-dose	D1 - - - - - - - - - - - - - - - - - D6	D7–D28	D90

Visit	Screening	Randomisation	Double-blind treatment period	Short-term FU	Long-term FU[c]
		Baseline includes D1 pre-dose[a]	Daily assessments while hospitalized[b]		

Figure 1. Study Design

[a] *Not more than 48 hours may elapse between arrival to hospital and administration of the first dose of study drug on D1. Once eligibility has been met, randomization can occur during screening or pre-dose on D1.*
[b] *Assessments are described in the Schedule of Procedures in Table 2.*
[c] *Telephone contact or searched from medical records if the patient cannot be contacted.*

Abbreviations: D=day; FU=follow-up

4.2 Criteria for Evaluation of the Safety and Efficacy

4.2.1 Criteria for Evaluation of Safety

- AEs up to D28, AEs occurring after D28 if the investigator considers there is a causal relationship with the study drug and all deaths up to D90.
- Physical examination to the extent available, vital signs and available laboratory results (biochemistry and haematology including pre-dose D1, D2-D7, D10, D14, D28/last day in hospital laboratory tests (Table 2)) while hospitalized.
- Immunogenicity as measured by anti-drug antibodies (ADA)

4.2.2 Criteria for Evaluation of Efficacy

Primary Efficacy Endpoint:

- Clinical status at D14 as measured by WHO 9-point ordinal scale:
  0 - No detectable infection;
  1 - Not hospitalized, no limitations on activities;
  2 - Not hospitalized, limitation on activities;
  3 - Hospitalized, not requiring supplemental oxygen;
  4 - Hospitalized, requiring supplemental oxygen;
  5 - Hospitalized, on non-invasive ventilation or high flow oxygen devices;
  6 - Hospitalized, on invasive mechanical ventilation;
  7 - Hospitalized, on mechanical ventilation plus additional organ support: renal replacement therapy, ECMO
  8 - Death

Secondary Efficacy Endpoints:

- Clinical status at D28 as measured by WHO 9-point ordinal scale (above)
- Secondary endpoints relating to the efficacy of IV IFN beta-1a treatment:
  - In-hospital mortality at Day 28 and Day 90
  - Overall (all-cause) mortality at Day 28 and Day 90

4.2.3 Criteria for Evaluation of Exploratory Endpoints

Exploratory Efficacy Endpoints:

- Exploratory endpoints relating to the efficacy of IV IFN beta-1a treatment in comparison to dexamethasone:
  - Incidence of ARDS
  - Incidence of AKI
  - Incidence of new mechanical ventilation
  - Days alive and free of renal support at Day 28
  - Days alive and free of ECMO at Day 28
  - Days alive and free of oxygen support at Day 28
  - ICU-days at Day 28
  - Days on mechanical ventilation on Day 28
  - Length of Hospital stay among survivors at Day 90

- Incidence of study treatment discontinuation and transition to an open label corticosteroid
- Association of efficacy outcome measures of study treatment with the vaccination status

Exploratory Laboratory Endpoints:

- Change in the treatment-specific exploratory biomarkers (MxA and CD 73) and PIMs (pre-dose on D1, D3, D5 and D7 for hospitalized patients) and Interferon beta (pre-dose on D1, D1 (5 minutes after study drug dosing), D3 and D7.
- Viral clearance for SARS-CoV-2 infection by D14 (viral RNA copy number pre-dose D1 and D4, D7, D10 and D14 (if subject's discharge is before D14, the specimen is obtained also on the day of discharge))
- A blood sample will be taken for pharmacogenetic analysis of the genetic susceptibility in responding to IFN beta-1a treatment. Under specific examination is SNP rs9984273 and surrounding area which is the glucocorticoid regulatory motif area of IFN alpha/beta receptor subunit 2 (IFNAR2). According to the previous Phase III Study (FPCLI002) this polymorphic site may determine responsiveness to IFN beta-1a treatment and outcome. The sub-groups carrying polymorphism in this region will be analysed separately for the Study outcome measures.
- Association of efficacy outcome measures of study treatment with the variant of SARS-CoV-2

4.3 Justification of the Study Design

This is a Phase II study to evaluate the safety and efficacy of IFN beta-1a in comparison to dexamethasone in the treatment of subjects with COVID-19. The study is designed as a double-blind, randomized, parallel-group, controlled, multicentre clinical study.

At present there is no approved pharmacological treatment for the prevention of ARDS. The only currently available treatment for mechanically ventilated COVID-19 patients is dexamethasone, but still COVID-19 mortality to ARDS remains high. Because of the lack of an effective pharmacological agent, glucocorticoids are widely used because of their anti-inflammatory properties. However, they may dampen natural anti-viral response of IFN beta signalling. Further, overlapping use of glucocorticoids may block IFN beta-1a from up-regulating CD73 on the lung endothelium. Therefore, the current approach is to investigate the use of IFN beta-1a before corticosteroids (or other medications with immunosuppressive activity) are indicated for COVID-19 and to prevent disease aggravation to ARDS.

The study target population is defined to subjects requiring oxygen supplementation (< 8 l/min) in order to comply with the treatment guidelines (https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/). The IFN beta-1a treatment arm is not to receive dexamethasone for study days D1-D6. This is justified with the anticipated anti-viral effects of IFN beta and clinical observations of severity of the disease associated with a deficiency in IFN signalling, and uncertainty of the benefit from dexamethasone in mild COVID-19 (see Section 2.6 for detailed justification for the study setting). However, should the study subjects condition worsen during the early course of the study, while the IMP is being administered (Study days D1-D6), the IMP can be discontinued and dexamethasone initiated according to the discretion of the attending physician, ideally after a discussion with the local study investigator, if the clinical condition of the patient permits it.

4.4 Study Population

The study population will consist of hospitalized patients due to confirmed SARS-CoV2 infection during the previous 7 days. Study subjects must meet all the inclusion criteria and none of the exclusion criteria to be enrolled in the study. The inclusion and exclusion criteria apply during screening and prior to administration of the first dose of study drug on D1.

4.5 Inclusion Criteria

The inclusion and exclusion criteria apply during screening and prior to administration of the first dose of study drug on study Day 1.

1. Age ≥18 years
2. Positive SARS-CoV-2 test by PCR or other diagnostic method within the past 7 days
3. Admission to hospital with respiratory symptoms of COVID-19 requiring hospital care and oxygen supplementation (≤ 8L/min)
4. Respiratory symptom onset no more than 7 days prior to hospital admission
5. Informed consent from the subject or the subject's personal legal representative or a professional legal representative must be available

4.6 Exclusion Criteria

1. Unable to screen, randomize and administer study drug within 48 hours from arrival to hospital
2. Systemic corticosteroid, baricitinib or tofacitinib (or other JAK-STAT signalling pathway inhibitors) therapy within 7 days prior to arrival to hospital or planned for the next days
3. Known hypersensitivity or contraindication to natural or recombinant IFN-beta-1a or its excipients, or to dexamethasone or its excipients
4. Currently receiving IFN-beta-1a therapy
5. Home assisted ventilation (via tracheotomy or non-invasive) except for Continuous positive airway pressure (CPAP) / Bilevel Positive Airway Pressure (BIPAP) used only for sleep-disordered breathing
6. Participation in another concurrent interventional pharmacotherapy trial during the study period
7. Decision to withhold life-sustaining treatment; patient not committed to full support (except DNR after cardiac arrest only)
8. Woman known to be pregnant, lactating or with a positive pregnancy test (urine or serum test)
9. Subject is not expected to survive for 24 hours
10. Subject has liver failure (Child–Pugh grade C)
11. Any clinical condition that in the opinion of the attending clinician or Investigator would present a risk for the patient to participate in the study

4.7 Confirmation of Patient Eligibility

To ensure appropriate enrolment into the study there will be a formal confirmation of eligibility process utilising the following procedure:

An electronic Case Report Form (e-CRF) with mandatory fields for completion and a checklist of inclusion and exclusion criteria; all items will need to be completed. The IWRS System will prompt the Investigator to confirm eligibility before allowing a patient to progress to randomization.

With this method, only those patients whose data are recorded as meeting eligibility criteria can be randomized.

4.8 Patient Withdrawal and Replacement

4.8.1 Discontinuation Criteria

Subject may withdraw from the entire study, including follow-up, at any time without penalty and for any reason without prejudice to their future medical care; they are not obliged to state their reasons for withdrawing. The decision to withdraw can be made by the subject or their Personal Legal Representative (PerLR) or Professional Legal Representative (PrfLR).

Subjects may be **withdrawn from the study** under the following circumstances:

- Protocol violations including non-compliance with study procedures or subject lost to follow-up
- Subject, PerLR or PrfLR request

The Investigator must ensure that the status page in the e-CRF for the **end of the study** is completed.

Necessity for concomitant glucocorticoid treatment during study days D1-D6 may occur (for treating conditions listed in the Table 1 or based on Investigator's judgement for other conditions necessitating **systemic (oral or intravenous)** glucocorticoid treatment) or deterioration of the study subjects condition due to COVID-19 may lead to IMP discontinuation and initiation of open label corticosteroids for COVID-19, neither of these are a condition for withdrawal.

Subject may be required to **withdraw from study drug** after discussion with the Sponsor and/or Investigator for the following reasons:

- Safety issues
- At the discretion of the attending physician if it is considered to be in the subject's best interest

Subjects who discontinue study drug should continue in the study for follow-up to D90. The Investigator must ensure that the status page in the e-CRF is completed and every effort should be made to minimize missing data.

In all cases, the reason(s) for withdrawal, including the primary reason, must be recorded in the e-CRF. If a subject is prematurely withdrawn from the study drug for any reason, the Investigator must make every effort to perform the evaluations described for the follow-up visits. Any on-going AEs should be followed up to resolution or D28 whichever is the sooner. D90 assessment for mortality should be sought to the extent possible. See also Sections 8.6.2 and 8.6.3.

If a subject (or their representative) withdraws consent and still agrees to undergo a final examination, this will be documented in the e-CRF and the Investigator's copy of the Informed Consent Document (ICD), which will be countersigned and dated by the subject (or PerLR or PrfLR).

Subjects who have discontinued or withdrawn their consent will not be replaced. Data and biospecimen collected before withdrawal will be used.

The study will be terminated if, in the opinion of the Sponsor, significant safety concerns arise during the conduct of the study.

4.8.1.1 Non-attendance of Follow-up Assessments

Attempts should be made to contact subjects discharged from hospital who do not attend their study follow-up assessments to ensure their well-being. In such cases, the subject will be contacted at least twice by telephone and once by letter to request that they attend the scheduled follow-up assessment. If subjects do not respond they will be considered as withdrawn at that time point (lost to follow-up). If a subject is lost to follow-up, wherever possible mortality data will be sought at all remaining mortality time points from alternative sources such as the subject's local physician or health records.

4.8.2 Replacement Policy

A screen failure subject is defined as any subject who did not comply with the inclusion and exclusion criteria during screening **and** prior to receiving the first dose of study drug. Subjects who become ineligible after consenting, and before treatment, will be deemed to be screen failures and will be replaced.

Subjects who complete screening and are randomized and receive the first dose of study drug will not be replaced even if later withdrawn or lost to follow-up.

It is possible that a subject may be randomized to a study group following successful screening but may become ineligible prior to administration of the first dose of study drug. For example, prior to the first dose of study drug a subject may deteriorate and require mechanical ventilation. Such subjects will be classed as screen failures and will be replaced.

Subject numbers (and randomization numbers if applicable) of screen failures will not be reallocated. A new subject will be enrolled and assigned the next available number.

4.9 Planned Sample Size and Number of Study Centres

It is planned to randomise and dose 140 subjects at approximately 5-15 centres in the USA and possibly also in other countries. See Section 7.4 for a discussion of sample size.

4.10 Subject Identification and Randomization

4.10.1 Subject Identification

A unique subject number (subject identification number) will be allocated to study patients. The subject number will be assigned at the study centre on enrolment (i.e., provision of written informed consent) in chronological order of screening and will be used throughout the study. If a subject is not subsequently randomized, their screening number will not be reallocated. Each screened subject will therefore have a unique identifier.

4.10.2 Randomisation Scheme

Subjects will be randomized on a 1:1 basis to FP-1201-lyo or dexamethasone. IWRS will be used to obtain randomisation details.

To ensure that conclusions are not dominated by data from a small number of centres, and also to obtain a broad spread of subjects and centres within the constraints of the inclusion/exclusion criteria, each centre will be allowed to include up to, but no more than, 30 patients.

Randomisation will be stratified by gender and age (under 70 years and 70 years and older). A sequence of randomisation numbers will be assigned to each study centre.

Refer to Section 5.4 for details of blinding and breaking the blind.

4.10.3 Randomisation of Subjects to Treatment

Randomisation of patients to treatment will occur during screening or on D1 after all screening procedures have been performed and eligibility for inclusion in the study has been confirmed. Each randomized subject will receive a unique randomisation number. Randomized subjects who terminate their study participation for any reason, regardless of whether study drug was taken or not, will retain their randomisation number.

The Investigator will use IWRS for randomisation of study subjects, details can be found in the study file.

4.11 Minorities and Women

No patients will be excluded on the basis of race, ethnicity, or sex. The Steering Committee and the Sponsor will monitor recruitment of minorities and women, and this recruitment will also be reviewed by the IDMC.

5 STUDY DRUG

5.1 Identity

Pharmacy manual contains the relevant information on the study IMP manufacturers, packagers and distributors.

5.2 Packaging, Labelling and Storage

FP-1201-lyo is provided by Faron to clinical sites. Dexamethasone (commercially available) and 0.9% Saline solution will be sourced locally by the sites.

FP-1201-lyo is secondary packaged in a carton, containing one vial. The dexamethasone packaging configuration may vary based on the source chosen by the clinical site.

Six investigational medicinal kits are provided per patient. These are reserved for each patient to cover the 6-day treatment period.

Labelling will be prepared to meet the local regulatory requirements.

All study drug supplies must be stored in accordance with the manufacturer's instructions, e.g., FP-1201-lyo kits are to be stored at 2–8°C (35.6°F–46.4°F) until dispensed to the patients. The study drug is to be stored in a securely locked area, accessible to authorised personnel only. The IMPs are dispensed and prepared only after approval by the Investigator or by a member of staff specifically authorised by the Investigator, or by a pharmacist, as appropriate.

5.3 Administration

Study IMP FP-1201-lyo (IFN beta-1a) 10 µg or dexamethasone 6 mg will be prepared for clinical application according to the instructions provided in the Pharmacy Manual. The IMP will be prepared by an unblinded site staff (i.e. Pharmacist) according to the randomization code and dispensed into a blinded syringe. The prepared IMPs will be administered as two intravenous bolus injections via a central or peripheral line. To maintain blinding at administration, every study subject will receive two separate bolus injections of IMP (either IFN-beta -1a/Saline, and another injection of

Saline/Dexamethasone). The exact time of both injections will be recorded and the injections will be followed with a 5 mL flush of sterile saline (not provided). Administration should be performed by blinded site personnel.

IMP injections will be given once daily for 6 days, unless the patient is discharged from the hospital. The injections should be given at the same time each day ±1 hour providing the patient's condition allows this. If for any reason this is not possible, the treatment should be given as soon as possible. The reason for the delay must be entered in the e-CRF. Subsequent doses should not be delayed and should revert to the original time schedule (e.g., if the D1 dose was at 13:00, the D2 dose was delayed and given at 17:00, the D3 dose should be given at 13:00 ±1 hour). No dose modifications or temporary cessations of IMP administration are allowed. If a delay is more than 12 hours, the patient must discontinue from study IMP, but all data must continue to be collected per protocol. Administration of a second 6-day course of study IMP is not permitted.

5.4 Blinding and Breaking the Blind

The study will be performed in a double-blind and randomized manner. IMP (IFN beta-1a and dexamethasone) will be prepared in identical syringes by an unblinded person, thereby enabling fully blinded conditions.

The treating physician is responsible for the medical care of the trial patient and the study set up allows the investigator/treating physician to rapidly break the treatment code in an emergency situation.

The study blind should only be broken in a medical emergency (where knowledge of the study drug received would affect the treatment of the emergency) or as a regulatory requirement (e.g., for SAEs or death). Note that there is no specific antidote or method of removing the study drug from the body (such as dialysis) and the best available care for the patient should be continued.

If the blind is broken, the date, time and reason must be recorded in the patient's e-CRF and any associated AE report. It is the responsibility of the investigator to promptly document and explain any unblinding to the sponsor/CRO.

Detailed instructions for the use of the IWRS in order to break the study blind for a patient are provided in a separate document that will be filed in the Site File and Trial Master File. As well as the IWRS, a backup system enabling unblinding of treatment is provided to the sites.

After a patient has been unblinded data collection should continue as per protocol.

Suspected unexpected serious adverse reactions (SUSARs), which are subject to expedited reporting, should be unblinded by the Pharmacovigilance group before submission to the regulatory authorities and IECs/IRBs (Independent Ethics Committee/Institutional Review Boards).

The overall randomisation code will be opened only for reporting purposes. This will occur when all D28 clinical data have been entered into the database and all data queries related to D28 have been resolved, and the assignment of patients to the analysis sets and database lock has been completed. After completion of the extended follow up of 90 days and resolving related queries the database is locked again for D90 analyses.

5.5 Drug Accountability

The Investigator is responsible for maintenance of accurate study drug accountability records throughout the study.

Each dispensing of study drug will be documented.

The Investigator is responsible for ensuring all unused medication is destroyed at the investigational site following the appropriate drug accountability procedures.

5.6 Compliance

The study drugs are administered intravenously at the study site, so it is not necessary to monitor patient compliance with the study drug regimen.

5.7 Previous and Concomitant Medications

Any medication the patient takes other than the study drug between screening and D28, including herbal and other non-traditional remedies, is considered to be a concomitant medication. All concomitant medications (for previous 7 days) must be recorded in the e-CRF except for nutritional and volume therapy, electrolyte support, vitamins and supportive therapies such as artificial tears, ointments, etc. The following information must be recorded in the e-CRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the e-CRF. If a patient is discharged from the hospital prior to D28 then the patient must be instructed that the Investigator should be informed about additional medication up to D28.

Concomitant medications or therapies that are considered necessary for the patient's welfare and that will not interfere with the study drug may be given at the discretion of the attending physician.

All patients in this study will be managed with supportive care measures according to the best practice established locally in study centre and in accordance with the treatment guidelines (https://www.covid19treatmentguidelines.nih.gov/therapeutic-management).

There are no prohibited co-medications in this study, except for systemic corticosteroids, baricitinib and tofacitinib (and other JAK-STAT signalling pathway inhibitors) as these agents have been demonstrated to have potential inhibitory effect on IFN beta.

6 STUDY CONDUCT AND ASSESSMENTS

6.1 General Considerations

The study will utilize standard clinical care laboratory assessments for safety, in order to avoid excessive sampling of blood in hospitalized subjects. Complete Blood Count (CBC), White Blood Cells (WBC) differential and biochemistry, for example, will be collected from clinical routine if available; if not then these will be collected as protocol specific assessments from pre-dose D1, D2-D7, D10, D14, D28/last day in hospital. The timing of the assessments is shown in the Table 2 Schedule of Procedures (below). Laboratory assessments needed for CBC, differential and chemistry should be taken on the timepoints indicated in the Table 2, if not available by clinical standard of care (i.e., analyses should not be duplicated if available by clinical routine).

For the purposes of this study, study day 1 (D1) is defined as the first calendar day (from midnight to the following midnight) of treatment with IFN beta-1a or dexamethasone. All days thereafter are defined as "Dn" (e.g., D2, D3, etc.) until D28.

Baseline assessments are defined as those assessments carried out in the screening period and pre-dose D1 (before the first dose of study drug on D1). Unless withdrawn from study or discharged from the hospital, all patients will receive study drug for 6 consecutive days (D1-D6). All assessments in the period up to D28 are only to be performed when a patient is in hospital. Study assessment at D14, D28 and D90 are performed by phone call if the patient is not any longer present at the hospital, or sought through records if the patient cannot be contacted. The end of the study will be the date of last patient/last visit at D90.

Table 2. Schedule of procedures and assessments

Procedure	Screening	D1 pre-dose	D1-D6	D7-D14[1]	D15-D27	D28 short-term follow-up[2]	D90 long-term follow-up (+/-7 days)
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Demographics	X						
Medical history	X						
Physical examination (incl. weight and height at screening)	X					X	
Pregnancy test in women of childbearing potential	X						
Review and documentation of available lung X-ray / CT scan	X						
Genetic sample		X[4]					
Randomization		X					
Administration of study drug			X				
Specimen collection[3]:							
MxA		X	X	X			
CD73		X	X	X			
PIMs[4]		X	X	X			
IFN beta		X	X	X			
ADAs		X				X	
COVID-19 test (if positive result of a test taken within the last 7 days is not available)	X						
COVID-19 for viral load PCR[5]		X	X	X			
Nasopharyngeal swab for virus variant analysis		X					
Biochemistry, CBC & Differential[6]		X	X	X		X	
Data collection from medical records:	X	X	X	X		X	X
WHO 9-point ordinal scale		X	X[1]	X[1]		X[1]	
Previous and concomitant medications and interventional therapies	X	X	X[1]	X[1]	X[1]	X[1]	
Clinical status assessments[7]		X	X	X	X	X	X
Vital signs[8]		X	X	X	X	X	
Adverse events[9]	X	X	X[1]	X[1]	X[1]	X[1]	X

All daily assessments should be obtained at the same time as D1 pre-dose assessment (+/- 2 hours), The specimen collections and assessments at pre-dose D1 should be within 4 hours prior to the administration of study drug.

1. *If the subject is not in the hospital, information to be collected by phone on D14 and D28*
2. *Short term follow-up; D28 or Day of discharge from hospital (whichever is earlier).*
3. *Blood collection for MxA, CD73 and PIMs will occur: pre-dose on D1, D3, D5; and on D7 for hospitalized patients (for IFN blood collection will occur: pre-dose D1, D1(5 minutes after D1 dosing), pre-dose on D3 and on D7). Blood collection for ADA will occur: pre-dose D1 and D28 or Day of discharge from hospital (whichever is earlier).*
4. *PIM = Potential Inflammatory and interferon signalling Markers on a protein and RNA level (Nanostring); DNA for genetic analyses will be extracted from the pre-dose PIM sample*
5. *A blood sample for PCR copy number quantification (SARS-CoV-2 test) will be collected on pre-dose D1 and on D3, D7, D10 and D14 (if subject's discharge is before D14, the specimen is obtained also on the day of discharge).*
6. *Biochemistry, CBC & Differential; Complete blood count & WBC differential (defined in Table 3) to be collected as performed locally and part of standard of care (pre-dose D1, D2-D7, D10, D14, D28/last day in hospital)*
7. *Includes the following assessments: Survival, hospital status, ICU status, renal support, ECMO, oxygen support, and mechanical ventilation. Assessments for D14 and D28 by phone for non-hospitalized subjects. Survival to be addressed from health records if patient cannot be contacted by phone (for D90 only survival and hospital status will be collected)*
8. *Vital signs pre-dose, 30 and 60 minutes (+/-10 minutes) after study drug administration (D1-D6), D7-D28 daily until discharge from hospital*
9. *Information collected by phone for non-hospitalized subjects. Survival to be addressed from health records if patient cannot be contacted by phone.*

6.2 Study Baseline Assessments

6.2.1 Screening

1. Informed consent
2. Inclusion and exclusion criteria
3. Demographic and admission data (including age, sex, race/ethnicity, pre-hospitalization level of care (according to ECOG/WHO Performance Status classification):
   - 0: able to carry out all normal activity without restriction
   - 1: restricted in strenuous activity but ambulatory and able to carry out light work
   - 2: ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
   - 3: symptomatic and in chair or in bed for greater than 50% of the day but not bedridden
   - 4: completely disabled; cannot carry out any self-care; totally confined to bed or chair
4. Medical history, including information on COVID-19 vaccination
5. Physical examination
6. Pregnancy test for women of reproductive age, if not performed in routine clinical care
7. Documentation of lung X-ray / CT scan (if available as part of standard clinical care), COVID-19 disease history (symptom onset, confirmatory SARS-CoV-2 test done, hospital admission date and time), Previous (7 days prior to arrival to hospital) and concomitant medications. Note that use of systemic glucocorticoids, baricitinib or tofacitinib (or other JAK-STAT signalling pathway inhibitors) seven days before hospital admission and at randomization is an exclusion criteria.
8. Adverse events

6.2.2 Pre-dose D1

1. Inclusion and exclusion criteria
2. Randomization (if feasible can be done also during screening)
3. Specimen collection including genetic sample per Table 2.
4. COVID-19 specimen collection (blood sample and nasopharyngeal swab)
5. WHO 9-point ordinal scale
6. Concomitant medications and therapies. Note that use of systemic glucocorticoids, baricitinib and tofacitinib (or other JAK-STAT signalling pathway inhibitors) at randomization is an exclusion criteria
7. Clinical status assessments
8. Vital signs
9. Adverse events

Screening assessments will be carried out after informed consent has been obtained and must be completed before the first dose of the study drug is administered. If a patient continues to meet all entry criteria (including negative pregnancy test and not receiving systemic glucocorticoids, baricitinib or tofacitinib (or other JAK-STAT signalling pathway inhibitors)), study drug will be administered. The first dose of study drug must be administered within 48 hours of admission to hospital, preferably as soon as possible.

The specimen collections and assessments at pre-dose D1 should be within 4 hours prior to the administration of study drug.

6.3 Study Assessments During Hospital stay

The following in-hospital data will be collected to assess trial efficacy and safety endpoints. Most data may be assessed by medical record review.

1. Administration of study drug once daily for 6 days
2. Close monitoring of vital signs for the 60 minutes following study drug administration
3. Specimen collection including COVID-19 sample per Table 2.
4. WHO 9-point ordinal scale
5. Concomitant medications and therapies
6. Clinical status assessments
7. Adverse events
8. Hospital discharge disposition.

The specimen collection should be prior to the administration of study drug and within +/-2 hours of the sampling time at D1.

If a subject has been discharged from the hospital but is re-admitted before Day 28 to the study site for COVID-19 associated reasons, the data for the visits assessments are recorded in CRF. Laboratory samples are not taken from re-admitted subjects, but, if possible, a serum sample for determining the viral load should be taken according to the timepoints in Table 2. The re-admission to hospital is reported as a SAE.

6.3.1 Vital Signs

Vital signs will be measured supine pre-dose on D1 (baseline) and daily while hospitalized as detailed in the Schedule of Procedures (Section 6, Table 2). The date and time of collection of each parameter will be recorded in the e-CRF.

Vital sign variables are:

- Blood pressure (BP; systolic, diastolic and mean; mmHg)
- Heart rate (HR; bpm): measured as per clinical practice in each hospital
- Total respiratory rate (breaths per minute)
- Temperature (°C): core temperature to be measured according to the site's usual practices for temperature recording and the site used for measurement should be recorded in the e-CRF

6.3.2 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Procedures (Table 2) and as applicable to subjects' condition.

A physical examination covering the major body systems (general appearance, head [ear, nose and throat], cardiovascular, eyes, respiratory, abdomen, urogenital, musculoskeletal, neurological, lymph nodes and skin) will be performed at screening (baseline) and following according to standard clinical practice and at D28 or Day of discharge from hospital (whichever is earlier).
At screening the physical examination will also include:

- Actual body weight measured or provided by the subject
- Actual height measured or provided by the subject.

6.3.3 Clinical status assessments

Clinical status assessments include survival, hospital status, ICU status, renal support, ECMO, oxygen support, and mechanical ventilation. Assessments for D14 and D28 are made by phone for non-hospitalized subjects. On D90 only survival and hospital status will be collected. Information will be sought from health records if patient cannot be contacted by phone.

6.3.4 Hospital Laboratory Assessments

6.3.4.1 Biochemistry and Haematology

The biochemistry and haematology analysis will be performed at the hospital laboratories of the individual Investigator sites. Copies of laboratory accreditation and relevant reference ranges will be provided to the Sponsor or representative prior to the analysis of the first patient sample at that site.

The laboratory variables measured in the study will be as detailed in Table 3.

Blood samples for determination of biochemistry and haematology (CBC, WBC Differential) will be taken at pre-dose on D1 (baseline value), D2-D7, D10 and D14 while the patient is in the hospital, and on D28 or the last day in hospital. The date and time of sample collection and the results will be recorded in the e-CRF (results for analysis performed routinely at the site on other days will also be recorded in eCRF).

Table 3. Biochemistry and haematology variables

Haematology:	Haemoglobin Haematocrit Erythrocytes MCV Platelets Leukocytes Differential counts of: Neutrophils Eosinophils Basophils Lymphocytes Monocytes	Biochemistry:	Albumin Creatine kinase Creatinine Bilirubin Alkaline phosphatase AST ALT Lactate Sodium (blood gas value acceptable) Potassium Bicarbonate Calcium (total calcium corrected for albumin level)
Pregnancy test:	In women with child-bearing potential only. A urine pregnancy test will be performed unless the patient is not producing urine in which case a serum pregnancy test will be performed instead		

Abbreviations: AST=aspartate transaminase; ALT=alanine transaminase; MCV=mean corpuscular volume.

6.3.4.2 COVID-19 confirmation test

A positive SARS-CoV-2 test result no older than 7 days should be available for inclusion in the study. The test can have been taken as part of the standard care or is performed for the study and the analyse method is according to the hospital laboratory routines. If information on the virus variant is available, it should be recorded in the e-CRF.

6.3.5 Central Laboratory Assessments

A maximum of 73 mL of blood will be taken for study-specific testing during the study in addition to sampling for routine local analysis of haematology and biochemistry variables. One nasopharyngeal swab is taken for determination of SARS-CoV-2 variants.

6.3.5.1 Anti-drug Antibodies to Interferon Beta-1a

For serum samples 5.0 mL of blood will be taken on D1 pre-dose (baseline) and D28 (or on last day in hospital or at withdrawal, if earlier) to determine the presence of anti-drug antibodies to IFN beta-1a.

Anti-drug antibody sample preparation and sample storage details are provided in the Laboratory Manual. It is essential that the actual time and date of collection of each antibody sample will be recorded in the sample collection form provided with the laboratory kits.

Anti-drug antibody samples will be analysed centrally at Wieslab AB, Malmö, Sweden.

6.3.5.2 Myxovirus Resistance Protein A

Whole blood samples (2 mL) will be taken pre-dose on D1, D3, D5 and on D7 for hospitalized patients for analysis of MxA levels. For details of sample preparation and storage refer to the Laboratory Manual. MxA samples will be analysed centrally at Wieslab AB, Malmö, Sweden.

6.3.5.3 Cluster of differentiation 73 (CD73), Potential Inflammatory Markers (PIMs) and Interferon Signalling Markers

Samples for the CD73 and PIM assessments will be collected pre-dose on D1 (baseline), D3, D5 and D7 for hospitalized patients as detailed in the Schedule of Procedures (Section 6, Table 2). Blood

samples of 2.5 mL will be collected for CD73; from these, serum samples will be prepared for the testing. Blood samples of 6.0 mL will be collected for PIM sample preparation; from these, plasma and cell samples will be prepared for the testing of the potential inflammatory markers, interferon signalling markers and genetics. Sample preparation and storage details are provided in the Laboratory Manual. It is essential that the actual time and date of collection of each sample is recorded in the sample collection form provided with the laboratory kits.

CD73 samples will be analysed centrally by Wieslab AB, Malmö, Sweden.

PIMs may include (but are not limited to): Interleukin-6, Interleukin-8, von Willebrand Factor, Hypoxia-inducible factor 1-alpha, Angiopoietin-2, IFN-γ, IP-10, MCP-1, and TNF-α, and interferon signalling markers. Inflammatory markers and interferon signalling will be analyzed both on a protein and RNA expression level using plasma and peripheral blood mononuclear cells (PBMCs) using Nanostring analyses. Inflammatory markers will be anaysed at MediCity Research Laboratory, University of Turku, Turku, Finland. Nanostring analyses will be performed at Wake Forest University Medical School after RNA and DNA extraction has been performed at MediCity for pharmacogenetics (see below).

6.3.5.4 Interferon beta (IFN beta)

A 2 mL venous blood sample for the determination of IFN beta in serum will be collected on pre-dose D1 (baseline), D1 (5 minutes after dosing), pre-dose D3 and D7 for hospitalised patients as detailed in the Schedule of Procedures (Section 6, Table 2). Blood sample preparation and sample storage details are provided in the Laboratory Manual. It is essential that the actual time and date of the collection of each sample is recorded in the sample collection form provided with the laboratory kits and in eCRF.

The post-dose sample taken 5 minutes after study drug administration on D1 must be taken from another extremity than the site where the study drug was administrated.

IFN beta in serum will be analysed centrally by Syrinx Bioanalytics Oy, Turku, Finland.

6.3.5.5 Pharmacogenetics

The genetic sample must be taken for a patient to enter the study. According to the previous Phase III Study (FPCLI002) there may be significant genetic variability in response to the investigational treatment. We specifically aim to investigate whether a specific genetic polymorphism rs9984273, which is the glucocorticoid regulatory motif area of IFN alpha/beta receptor subunit 2, defines responsiveness to treatment, and whether this sub-groups should be a targeted population for the investigational medicinal product.

PIM sample collected pre-dose on D1 will be used for genetic analyses; sample preparation and sample storage details are provided in the Laboratory Manual. Genetic analyses will be done at MediCity Research Laboratory, University of Turku, Turku, Finland.

The samples and data for genetic analysis in this study will be coded. Samples will not carry any personal identifiers. DNA samples will be destroyed 15 years after completion of this study.

6.3.5.6 SARS-CoV-2 viral burden

A 2.5 mL blood sample for SARS-CoV-2 viral burden in serum are collected on pre-dose Day 1 and on Day 3, Day 7, Day 10 and on Day 14 (only for hospitalized patients, if patient's discharge is before D14, the specimen is obtained also on the day of discharge). The date and time of sample collection will be recorded in the-CRF.

6.3.5.7 SARS-CoV-2 variants

A nasopharyngeal swab is taken on pre-dose Day 1 for central analysis of variants of SARS-CoV-2.

6.3.6 Lung X-ray/CT scan

For the purpose of diagnostic accuracy, the study will utilize only documentation of lung X-ray/CT scan performed as part of standard clinical care; separate X-ray/CT scans are not performed for study purpose. No separate imaging manual exists for the Study, and images will not be collected.

6.4 Post-Discharge Assessments

Patients will be contacted at D14, D28 (if discharged; assessment window of +/- 3 days permitted, but with exact assessments for D14 and D28 conditions) and D90 (if discharged; assessment window of +/- 1 week permitted) to assess for health status, including mortality. At D14 and D28 the patient will be assessed on changes in the concomitant medications and on possible adverse events. On D90 only survival and hospital status will be collected. At the time of enrolment, subjects will be asked to provide at least two methods of contact, as well as contact information for a caregiver, to facilitate contact at Day 90. Patients who cannot be reached by phone will be mailed a follow up letter. The information is sought through records if the patient cannot be contacted.

Please see section 6.3. for patients that have been discharged from the hospital but are re-admitted due to COVID-19 before D28 to the study site.

6.5 Withdrawal Prior to Day 28

For patients withdrawing from the study, procedures for the last day of study involvement should be followed.

In the case of an ongoing AE, appropriate safety evaluations and/or additional tests may be performed at any time when clinically indicated at the discretion of the attending physician or Investigator, until resolution or Day 28, whichever is first. Any ongoing AEs should be followed up to resolution or Day 28, whichever is the sooner.

If the patient refuses to have any of the above assessments, or if the patient is lost to follow-up, then this should be noted in the e-CRF. If a patient is lost to follow-up, wherever possible, mortality data will be sought from alternative sources, such as the patient's local physician or available national databases and all data obtained reported as SAEs.

6.6 Safety Variables

6.6.1 Adverse Events

6.6.1.1 Collection of Adverse Events

It is the responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by observation, by spontaneous unsolicited reports of patients, and, where appropriate, by routine open questioning, e.g., "How have you felt since I last saw you?"

6.6.1.2 Definitions

Definitions of AEs and SAEs and their documentation and reporting within this study follow International Conference on Harmonisation (ICH) Good Clinical Practice, European Union, and national regulations and requirements.

An AE is defined as any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

All AEs up to D28 are collected. AEs occurring after D28 should be reported to the Sponsor if the Investigator considers there is a causal relationship with the study drug. All AEs up to D90, which lead to death, are reported as SAEs. Concomitant illnesses, which existed before entry into the study, will not be considered AEs unless there is any deterioration from baseline that is considered clinically relevant or significant during treatment or follow-up period until D28. All AEs must be documented, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, reported by patient).

Pre-existing conditions will be recorded in the e-CRF on the Medical History or appropriate page.

A TEAE (Treatment-Emerged Adverse Event) is defined as an AE that begins or that worsens in severity after at least one dose of study drug has been administered up to D28.

See 6.1 for the schedule of collection of adverse events

6.6.1.3 Assessment of Adverse Events

It is recognised that the patient population in the hospital will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of their underlying disease and the impact of standard therapies. These will not necessarily constitute an AE unless they require intervention, lead to discontinuation of blinded study drug or are considered to be of concern in the Investigator's clinical judgement.

Each AE will be assessed by the Investigator with regard to the following categories:

6.6.1.3.1 Seriousness

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. This means that the patient is at risk of death at the time of the event. It does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalisation but that may jeopardise the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate. However, all deaths up to D90 will be reported as a SAE.

"At any dose" does not imply that the patient is receiving study treatment at the time of the event. Study drug doses may have been given during treatment cycles or interrupted temporarily prior to the onset of the SAE, but may have contributed to the event.

6.6.1.3.2 Intensity

Investigator will be responsible for the assessment of severity, using the categories of mild, moderate or severe to describe each AE as:

- **Mild:** Does not interfere with patient's usual function
- **Moderate:** Interferes to some extent with patient's usual function
- **Severe:** Interferes significantly with patient's usual function

Note the distinction between serious and severe AEs. **Severe** is a measure of intensity whereas an event must meet one of the criteria for serious events listed in Section 6.6.1.3.1 to be considered **serious**; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 6.6.1.3.1.

6.6.1.3.3 Causality

The Investigator will assess the causality/relationship between the study drug and the AE and record that assessment in the e-CRF. Causality will be assessed as:

- **Not related:** AE is obviously explained by another cause; OR the time of occurrence of AE is not reasonably related to administration of the study drug
- **Possibly related:** Study drug administration and AE occurrence are reasonably related in time; AND AE is explained equally well by causes other than study drug
- **Probably related:** Study drug administration and the occurrence of the AE are reasonably related in time; AND the AE is more likely explained by exposure to study drug than by other mechanisms

The most likely cause of an AE (e.g., disease under treatment, concomitant disease, concomitant medication, other) will be indicated in the e-CRF with details of the concomitant disease or medication or other cause.

6.6.1.3.4 Adverse events related to laboratory assessments

Abnormal laboratory findings (e.g., biochemistry, haematology, urinalysis) or other abnormal assessments (e.g., vital signs) that are judged by the Investigator as clinically significant will, if certain requirements are met, be recorded as AEs or SAEs. Clinically significant abnormal laboratory findings or other abnormal assessments that meet the definition of an AE or SAE and are detected during the study, or are present at baseline and significantly worsen following the start of the study, will be reported as AEs or SAEs.

The Investigator will exercise their medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant and as such an AE.

6.6.1.4 Recording Adverse Events

AE reporting will extend from signing of informed consent. AEs occurring after D28 should be reported to the Sponsor by the Investigator if the Investigator considers there is a causal relationship with the study drug. However, all deaths will be recorded and reported as SAEs throughout the study (up until D90).

All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to study drug, action taken with the study drug, outcome, and whether the event is classified as serious.

Recording a diagnosis (when possible) is preferred to recording a list of associated signs and symptoms. However, if a diagnosis is known but there are associated signs or symptoms not generally attributed to the diagnosis, the diagnosis and each sign or symptom must be recorded separately.

6.6.1.5 Reporting Serious Adverse Events

According to applicable US and European Union regulations and requirements, an SAE must be reported to the Sponsor from the trial site as soon as possible **within 24 hours** of becoming aware of the SAE. A medically qualified person at the trial site identified on the Delegation of Authority Log with this responsibility must assess the SAE. Any member of the clinical trial site staff can assist in reporting an initial SAE. The Principal Investigator or delegated sub-investigators are responsible for the SAE reporting procedures at the site during the trial, and must always sign-off on each SAE even if other site staff have reported the event on behalf of the investigators. A delegation log at each trial site will clearly show delegation of responsibilities regarding SAE reporting.

The SAE reporting is done via the eCRF system. Paper forms are available as back-ups.

The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report and the seriousness and the causal relationship of the event to study treatment will be evaluated. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference document (Investigator Brochure). Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

If consensus on the assessment cannot be reached between the parties (e.g., Investigator and Sponsor/Sponsor's delegate), all opinions will be provided in the Council for International Organizations of Medical Sciences Form I report and reporting to the CA and IEC/IRB should be based on the highest degree of causality provided.

Details for reporting SUSARs can be found in Section 6.6.1.7.

All SAEs will be recorded that occur between signing of informed consent and D28. Events occurring after D28 and coming to the attention of the Investigator should be reported only if they are considered in the opinion of the Investigator to be causally related to the investigational drug. However, all deaths up to D90 will be reported as SAEs.

All SAEs occurring as described above, must be reported **within 24 hours**.

The minimum information required for an initial report is:

- Details of person sending the report (i.e., name and address of Investigator)
- Patient identification details (screening/randomization number, age, sex, NOT patient name)
- Protocol number
- Description of SAE
- Causality assessment

However, all points on the SAE report should be covered in the initial report.

After receipt of the initial report, Pharmacovigilance (PV) will review the information and, if necessary, contact the Investigator to obtain further information for assessment of the event. PV CRO will be responsible for all information processing and reporting according to local legal requirements.

Detailed instructions concerning SAE reporting procedures will be described in a Safety Management Plan written by PV CRO. SAE Report Form and contact information for reporting SAEs will be provided to the sites.

6.6.1.6 Follow-up of Adverse Events

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until: the AE has resolved or any abnormal laboratory values have returned to baseline, or stabilised at a level acceptable to the Investigator and Medical Monitor; there is a satisfactory explanation for the changes observed; the follow-up period is completed (D90) or the patient is lost to follow-up; or the patient has died.

6.6.1.7 Suspected Unexpected Serious Adverse Reactions

Any AE that is serious, associated with the use of the study drug, and unexpected (SUSAR) has additional reporting requirements, as described below.

- If the SUSAR is fatal or life threatening, associated with use of the study drug and unexpected, regulatory authorities and IECs/IRBs must be notified **within 7 calendar days** after the Sponsor learns of the event. Additional follow-up information (cause of death, autopsy report and hospital report) should be reported **within an additional 8 days** (15 days total).
- If the SUSAR is not fatal or life threatening but is otherwise serious, associated with the use of the study drug and unexpected, regulatory authorities and IECs/IRBs must be notified **within 15 calendar days** after the Sponsor learns of the event.

The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of patients. Follow-up information may be submitted if necessary.

The Sponsor will also provide annual safety updates to the regulatory authorities and IECs/IRBs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

6.7 Pregnancy

Pregnancy is an exclusion criterion, and a pregnancy test is performed in all women of childbearing potential at screening. Owing to the nature of the study involving short (6-day) treatment with the study drug in a hospital setting, it is not practically possible for women to become pregnant during treatment and for there to be any foetal exposure to the study drug. Study subjects and their partners are advised not to become pregnant for 2 months after the study drug exposure and to use appropriate contraception. Any pregnancy during the study (for 2 months after the study drug exposure) that becomes to the knowledge of an investigator during the study, should be reported as an SAE and followed-up for the outcome. Any pregnancy, which onset is after 2 months from the study drug exposure, until the end of the study, will be reported (as a non-SAE) and followed-up for the outcome.

7 STATISTICAL METHODS

The statistical considerations summarised in this section outline the plan for data analysis of this study.

The main analysis and reporting will use D14 and D28 data after last study subject has completed D28 assessment and the data has been verified and locked. D90 follow-up data is analysed separately.

Before unblinding/database lock, a separate Statistical Analysis Plan (SAP) will be finalised, providing detailed methods for the analyses outlined below. Before the conduct of interim analysis, an Interim Analysis (IA) plan will be finalised. After the clinical parts of the study have been completed, a blinded review of the data will be undertaken according to the SAP/IA plan. This review will make decisions regarding: the handling of missing data and data for withdrawn patients; and the definition of the Per-Protocol Set (PPS) at the patient level.

Any deviations from the planned analyses will be described and justified in the final integrated study report.

7.1 Study Patients

7.1.1 Disposition of Patients

Disposition and reasons for discontinuation will be summarised for all patients together with study drug exposure and study duration by treatment group.

The number and percentage of patients entering and completing each phase of the study will be presented by treatment group. Reasons for withdrawal pre- and post-randomization will also be summarised.

The disposition of patients will also include information on the number and percentage of patients who:

- completed study drug and follow-up
- withdrew from study drug but completed follow-up
- withdrew from study drug and from follow-up

7.1.2 Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be classified as “minor” or “major” in conjunction with the Sponsor and Medical Monitor. Relevant major deviations from the protocol will lead to the exclusion of that patient from the PPS. Deviations will be defined prior to unblinding.

7.1.3 Analysis Sets

The following analysis sets will be defined for statistical analysis:

The **Full analysis set (FAS)** will consist of all randomized patients who have been received at least one dose of study drug. If a randomized subject becomes ineligible before dosing the subject will be replaced and is excluded from the FAS. The primary efficacy analyses will be based on this data set. Patients will be included in the analysis according to the treatment to which they were randomized.

The **Per-Protocol Set** (**PPS**) will consist of patients in the FAS excluding patients with major protocol violations. A list of major protocol violations relevant for excluding data from the PPS will be detailed in the SAP before the interim analysis. The precise definition of the PPS at the patient level will be identified at the blinded data review meeting before the interim and final analyses.

Statistical analyses for the primary and secondary endpoints will be performed on both the FAS and PPS.

The **safety set** will consist of all patients who receive at least one dose of study drug. All safety and tolerability analyses will be based on this analysis set. A patient who receives the wrong treatment according to their randomisation will be analysed for safety and tolerability in the treatment group corresponding to the treatment received.

Statistical analyses for the primary and secondary endpoints will be performed on both the FAS and PPS. The primary efficacy endpoint analysis will be based on the FAS; a secondary analysis will also be performed based on the PPS to assess the sensitivity of the analysis to the choice of analysis set. All safety analyses will be based on the safety set. Demographic and baseline characteristics will be evaluated for the FAS.

7.2 General Considerations

All statistical tests will be two sided and will be performed at the significance level of 0.05, unless otherwise stated.

Continuous data will be summarised by treatment group using descriptive statistics (number, mean, median, standard deviation [SD], minimum and maximum). Categorical data will be summarised by treatment group using frequency tables (frequencies and percentages).

7.2.1 Analysis and Data Conventions

7.2.1.1 Definition of Baseline

The baseline assessment, where relevant, will be the latest available valid pre-dose assessment.

7.2.1.2 Visit Windows

Assessments made outside of protocol-mandated windows will be displayed according to the e-CRF assessment recorded by the Investigator.

7.2.1.3 Unscheduled Assessments

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than one laboratory value is available for a given visit, the first valid observation will be used in summaries and all observations will be presented in listings. It is noted that invalid laboratory data will not be used (from haemolysed samples, mishandled samples, quantity not sufficient, or other conditions that would render values invalid).

7.2.1.4 Missing Data Handling

In general, data will not be imputed for the primary efficacy analysis or the safety analysis. For other efficacy analyses, where relevant, imputations will use the last observation carried forward method for patients in the analysis. Additional details will be given in the SAP.

7.2.1.5 Intercurrent events

Use of open label corticosteroids (i.e., discontinuation of study IMP during D1-D6 and initiation of corticosteroids due to deterioration of the study subjects' condition, or initiation of corticosteroids D7 onwards) is an intercurrent event anticipated to affect the study outcomes. The primary analysis is planned to follow the treatment policy strategy (using FAS dataset). As sensitivity analyses, also other strategies under the estimands framework (ICH E9 (R1) addendum) will be applied to account

for this intercurrent event. Details of these analyses will be described in SAP. The frequency and magnitude of the effect of the use of corticosteroids to the study outcomes will be also evaluated during the planned Interim Analysis.

7.3 Demographics, Medical History, Baseline Characteristics and Concomitant Medications

Baseline assessments will consist of those assessments carried out in the screening period and those carried out prior to the first dose of study drug on D1.

Demographic and baseline characteristics will be summarised by treatment group and overall. No formal statistical comparisons will be undertaken to compare treatment groups for any of these parameters.

Demographic data, medical history, concomitant disease and concomitant medication will be summarised by descriptive statistics (number, mean, SD, median, minimum and maximum) or frequency tables, overall and stratified by treatment.

A medication given prior to the first injection of study drug will be classified as a prior medication. A medication given with or after the first injection of study drug will be classified as concomitant. Prior medications continuing during the study will be labelled accordingly in the listings.

7.4 Determination of Sample Size

140 patients will be randomised 1:1 for active: comparator. Conditional Power re-assessment will be conducted at interim analysis after circa 70 patients have been enrolled and followed up for the primary efficacy endpoint variable. The primary variable is the clinical status at Day 14 using the WHO 9-point scale (0=no detectable infection to 8=death). It will be analysed using ordinal logistic regression model comparing the odds of having better clinical status (smaller number in the 9-point scale) at Day 14 between treatment groups. The sample size is based on an assumption of odds ratio of 0.43 between groups leading to a power of 80% with 70 evaluable patients per group. In the interim analysis the conditional power will be calculated based on the observed result and the sample size will be increased in case the conditional power is in the predefined promising zone. The details of interim analyses will be given in IDMC charter created at the study initiation and in an interim analysis plan which will be finalised before breaking the blind for interim analysis.

7.5 Efficacy Analyses

7.5.1 Primary Efficacy Analysis

For the Primary Efficacy Endpoint the following hypotheses will be tested:

- Null hypothesis H_0: the WHO OSCI at D14 in the IFN beta-1a treatment group is equal to that in the control group
- Alternative hypothesis H_A: the WHO OSCI at D14 in the IFN beta-1a treatment group is not equal to that in the control group

The primary analysis of this endpoint will be based on the FAS, with a sensitivity analysis based on the PPS providing supportive information. Each of these analyses will be undertaken at the two-sided significance level of 0.05. For powering of the primary efficacy endpoint see chapter 7.4.

The primary variable will be analysed using ordinal logistic regression model comparing the odds of having better clinical status (smaller number in the scale from 0 to 8) between the groups. The primary model will include baseline OSCI score and age, gender and ethnicity as a covariate. In

addition, also a model without covariates will be applied and the results provided as sensitivity analysis. The percentages in each category for both groups will be presented descriptively including 95% confidence intervals.

Primary endpoint as well as other efficacy endpoints will also be presented for key predefined subgroups of patients (such as SNP rs9984273, see Section 4.2.3) together with 95% CIs for the difference in those rates to supplement the investigation of homogeneity.

7.5.2 Secondary Efficacy Analyses

For the Secondary Efficacy Endpoint WHO OSCI score at Day 28 will be analysed in a similar ordinal logistic regression model than the primary endpoint.

The primary analysis of the mortality endpoints (in-hospital and overall (all-cause) mortality at Days 28 and 90) will be based on the FAS and will be undertaken using COX proportional hazards regression model adjusting for age, gender and ethnicity key baseline characteristics. This analysis will be repeated using the PPS as a sensitivity analysis. Hazard ratios comparing the treatment groups will be reported using 95% CI for these endpoints. Data for these efficacy endpoints will also be presented for key predefined subgroups of patients (such as SNP rs9984273, see Section 4.2.3 together with 95% CIs for the difference in those rates to supplement the investigation of homogeneity.

7.5.3 Exploratory Efficacy Endpoints

Incidence of ARDS and AKI

The binary variables for incidence of mechanical ventilation, ARDS and AKI (until Day 28) will be analysed with logistic regression model with similar covariates than used for the primary endpoint analysis. Odds ratios comparing the treatment groups will be reported using 95% CI for these endpoints.

Days Free of Renal Support, ECMO, Oxygen support, Mechanical ventilation, ICU and Hospital Care

Renal support -free days alive are defined as the number of days in the first 28 days after the first dose of study drug that the patient is alive and free of renal support (renal replacement therapy).

In similar fashion days alive and free from mechanical ventilation, ECMO, oxygen support, length of hospital and of ICU stay at D28 will be evaluated.

General linear mixed model will be used for the analysis of these endpoints. However, if there is no valid distribution assumption, then Wilcoxon rank sum test will be applied. The statistical methods to be used for these exploratory efficacy endpoints will be detailed further in the SAP.

Incidence of study treatment discontinuation and transition to an open label corticosteroid

The frequency and the onset date of the use of open label corticosteroids between the groups will be analyzed with general linear mixed model. However, if there is no valid distribution assumption, then Wilcoxon rank sum test will be applied. The statistical methods to be used for these exploratory efficacy endpoints will be detailed further in the SAP.

Laboratory variables

Descriptive statistics (mean, median, SD, minimum and maximum) for laboratory variables will be obtained and tabulated by treatment group. The statistical methods to be used for the analysis of laboratory exploratory endpoints will be detailed in the SAP.

SARS-CoV-2 variant and SARS-CoV-2 vaccination status

Effect of SARS-CoV-2 variant and SARS-CoV-2 vaccination status on the primary and secondary efficacy endpoints will be explored using these variables as subgroups and presenting the results for each subgroup with 95% confidence intervals.

7.6 Safety Analyses

These summaries will be based on the safety set. The presence of anti-drug antibodies to IFN beta-1a at D28 will be summarised by treatment groups in terms of counts.

7.6.1 Adverse Events

AEs and SAEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by system organ classes and preferred terms. In the event that intensity or relationship of an AE to the study drug is missing, a worst-case scenario will prevail (severe in intensity or probably related). Only TEAEs (AEs that occur after the first study drug administration, that were not pre-existing or that increased in intensity) will be included in the summary tables. Counting will be performed for patients and events separately. Patients experiencing the same event more than once will have that event counted once within the corresponding system organ class and with a unique preferred term. All AEs will be included in the data listings. Listings of SAEs, of AEs leading to study drug withdrawal and of AEs leading to death will also be provided.

7.6.2 Independent Data Monitoring Committee

An IDMC will be established for the study to monitor safety (see Section 8.8).

8 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

8.1 Data Quality Assurance

The Sponsor or Sponsor's designee will verify the qualifications of each Investigator, inspect the site facilities and inform the Investigator of their responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded in the e-CRF for this study must be consistent with the patients' source documentation (i.e., medical records).

8.1.1 Database Management and Quality Control

All study-related data generated by site personnel will be captured electronically at each study centre using the e-CRF.

Central laboratory assays (e.g., PD, genetic analyses) will be managed by the central laboratories and results will be transferred for inclusion in the study analysis database.

Once the e-CRF clinical data have been submitted, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, and the time and date will be logged to provide an audit trail.

The specific procedures to be used for data entry and query resolution using the e-CRF will be provided to study sites in CRF completion instructions. In addition, site personnel will receive

training on the e-CRF. Once the source data verification is complete and all queries are closed, Data Management will freeze the e-CRF page.

8.2 Case Report Forms and Source Documentation

All data obtained during this study must be promptly entered in the e-CRF. All source documents from which e-CRF entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments and x-ray/CT scans.

Data that will be entered directly into the e-CRF (i.e., for which there is no prior written or electronic record) are considered to be source data.

The e-CRF entries for each patient will be checked against source documents at the study site by the CRA.

8.2.1 Data Collection

The Investigators (and appropriately authorised staff) will be given access to an online web-based electronic data-capture system that is compliant with US Food and Drug Administration Title 21 Code of Federal Regulations Part 11. This system is specifically designed for the collection of clinical data in electronic format. Access rights to the electronic data-capture system will be carefully controlled and configured according to each individual's role throughout the study. Only the Investigator and authorised staff will be able to enter and correct data in the e-CRF. Protocol deviations can be recorded within the e-CRF system also by the Sponsor/CRO CRA.

The e-CRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. Therefore, the e-CRF is to be completed as soon as possible during or immediately after the patient's visit or assessment. The Investigator must verify that all data entries in the e-CRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the e-CRF.

Computerised data-check programs and manual checks will identify any data discrepancies for resolution. Corresponding queries will be generated in the system and the site will be informed online about new issues to be resolved. All discrepancies must be resolved online directly by the Investigator or by staff authorised to do this by Delegation of Authority.

After completion, the Investigator will be required to electronically sign off the clinical data.

8.3 Access to Source Data

During the study, the Sponsor/CRO site CRA will make regular site visits to review protocol compliance, conduct source data verification by comparing e-CRF entries and individual patient's medical records, assess drug accountability and management, assess laboratory procedures and ensure that the study is being conducted according to pertinent regulatory and protocol requirements. The review of medical records will be performed in a manner that ensures patient confidentiality is maintained. Remote review of source data can be performed if permitted by the study site.

Source data verification will be required to monitor the progress of the study. Moreover, regulatory authorities in certain countries, IECs/IRBs and/or the Sponsor's Clinical Quality Assurance Group or designee may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator must assure the

CRO and the Sponsor that they will provide the necessary support at all times. Also U.S. Department of Defense providing funding for the study can access source records as part of study oversight.

8.4 Archiving Study Records

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g., signed Patient Information and Consent Documents, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of eCRFs etc.) are stored in secure archives for 25 years after the end of the trial. However, these documents should be retained for a longer period if required by applicable legal requirements. The Sponsor's approval is required prior to transfer or destruction of the documents.

8.5 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the Good Clinical Practice guidelines of the ICH and the Declaration of Helsinki (Declaration of Helsinki 2013). The study will also be carried out in keeping with local legal requirements.

8.6 Informed Consent

The Investigator at each investigational site is responsible for ensuring that written informed consent for study participation is given by each patient or their legal representative prior to collection of study data and administration of the study drug. Unless the study site is in a country where consent can only be obtained from the patient but can be waived and obtained retrospectively, according to local IEC rules, the Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. If consent has not been obtained, a patient cannot be enrolled into the study.

Consent will be sought from the patients themselves, if this is possible. However, it is recognised that some patients may be unable to give written informed consent themselves due to severity of the clinical condition. For these patients, written informed consent will be sought from a PerLR or PrfLR. The PerLR may be a relative, partner or close friend. Any country-specific guidance on who may act as a PerLR will be followed. If the patient is unable to give consent and no PerLR is available then a doctor at the investigational site who is not connected with the conduct of the study may act as a PrfLR (in countries where this process is acceptable). Any country-specific guidance on who may act as a PrfLR will be followed. In some countries, according to IEC rules, consent can only be obtained from the patient. In these countries, if the patient is unable to give consent, their relatives and the patient's own family doctor will be informed about the study. Consent from the patient will be obtained as soon as the patient is able to understand the study and sign the consent form. The appropriate guidances and laws will be followed for each country participating in the study.

If a protocol amendment is required, the ICD may need to be revised to reflect those changes. If the ICD is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all patients (or their representatives) subsequently enrolled in the study as well as those currently enrolled in the study where relevant.

8.6.1 Consent Procedure

The person giving consent will be informed about the study by the Investigator or by a member of the research team to whom the Investigator has delegated the consent process. The patient will also be given a copy of the ICD.

To provide all the necessary information, clinical study information and ICDs are quite lengthy. For this study, dependent on country or site specific regulations, an abbreviated initial section of the ICD will provide a short summary of key information, followed by the detailed information for those interested in receiving further information.

The patient, PerLR or PrfLR must be given adequate time to consider their decision about entering the study. However, the requirement to initiate study treatment within 48 hours of admission to hospital meeting inclusion criteria will of necessity be a consideration.

In all cases, the patient, PerLR or PrfLR will be asked to sign two copies of the ICD, which will then be countersigned by the Investigator or the member of the study team to whom obtaining consent has been delegated. One copy of the document will be retained by the person giving consent (patient, PerLR or PrfLR). The second copy will be photocopied. The photocopy will be placed in the patient's medical records, if allowed by hospital's regulations, and the original will be retained in the Investigator Site File. Alternative practical arrangements, including electronic consent processes, might be used due to e.g., COVID-19 restrictions at the hospitals.

A similar procedure will be followed for retrospective patient informed consent, which will be an additional section at the end of the ICD (see Section 8.6.2).

The terms of the consent and details of the informed consent discussions should be recorded in the subject's medical notes; this should include the date the consent was given and the short name of the study or protocol code.

8.6.2 Retrospective Patient Informed Consent

Patients for whom consent was given by a PerLR or a PrfLR will be informed of their participation in the study by the Investigator or by a member of the research team to whom the Investigator has delegated the consent process. This process will take place once the patient has regained the capacity to understand the details of the study. The timing of this process will thus vary between patients. However, every attempt to obtain retrospective consent must be made when the patient's condition is appropriate. If a patient's condition has precluded the re-consent process occurring by D90 (3 months), then no further attempts will be made to re-consent the patient.

Once informed, patients will be given an adequate amount of time to consider their decision to consent to continued participation in the study and to sign the re-consent section of the ICD.

If the patient does not give retrospective consent then the patient will be informed of the importance to collect the data and that the data collected from the patient to that time point will be entered into the analyses as the withdrawal does not extend to the data already obtained during the time the subject was enrolled. Blood samples already collected up to the time of withdrawal will be analyzed. Genetic samples collected will be analysed per protocol. No further data will be collected; the patient will be considered as withdrawn and the reason for withdrawal will be 'retrospective consent not given'.

8.6.3 Withdrawal of Consent

Patients may withdraw or be withdrawn (by the PerLR or PrfLR) from the study at any time, for any reason and such a decision will not affect the ongoing care given to the patient. Data recorded and biospecimen collected up to the point of withdrawal will be included in the study analyses.

If a patient or PerLR/PrfLR requests termination of the administration of study drug during the treatment period, then the administration of study drug will be stopped but the patient will continue in the study and all follow-up assessments will be performed.

If a patient or a PerLR/PrfLR withdraws consent during or after the treatment period then the administration of study drug will be stopped and no further active study assessments will be performed from that point on. However, permission will be sought to access the patient's medical records to obtain data relevant to the study and safety evaluation (e.g., mortality, etc.). If a patient (or their representative) withdraws consent and still agrees to undergo a final examination, this will be documented in the e-CRF and the Investigator's copy of the Informed Consent Document (ICD), which will be countersigned and dated by the subject (or PerLR or PrfLR).

8.7 Protocol Approval and Amendment

For the study to start, all required documentation must be approved by the IEC/IRB and Competent Authority, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, substantial amendments must be written, receive approval from the appropriate personnel, and receive IEC/IRB/competent authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

8.8 Independent Data Monitoring Committee

An IDMC will be established for the study. The IDMC and associated parties (CRO, PV, Data management and the Sponsor) will function under the terms of an IDMC Charter. The IDMC will comprise three members, including one independent biostatistician and two senior clinicians with significant experience in clinical management of critically ill patients and who are not involved in the study. The duty of this IDMC is to protect the safety interests of patients and all others who may possibly be exposed to the study drug and to make recommendations to the Sponsor. The IDMC will review ongoing safety data (all SAEs) in an unblinded manner. IDMC meetings are scheduled to take place after the data has been received for the last patient of approximately 20 and 40 subjects and at an interim analysis at 70 subjects who either have completed 14 days in the study following their first dose of study medication or have been withdrawn for any reason (including death). The IDMC will not review efficacy data, other than how it relates to the safety of the therapy. However, the IDMC will review the efficacy data at interim analysis after 70 evaluable subjects, where the sample size re-assessment will be conducted. From each meeting, the IDMC will make a blinded recommendation to the Sponsor regarding the study to continue without change, modify study or enrolment to be placed on hold, or study termination. The sponsor is obligated to inform the study sites, IECs/IRBs and Competent Authorities of the IDMC recommendations according to country specific requirements.

8.9 Steering Committee

A Steering Committee will be established for this study. Members of the Steering Committee may also be Investigators or Sub-investigators. Face-to-face meetings will be held as determined by need. Routine business will be conducted by email, post or teleconferencing.

The Steering Committee will provide advice and support to the study in matters concerning:

- Communicating with sites (e.g., in the instance of recruitment or quality issues)
- Oversight of the progress of the study

- Informing and advising on all aspects of the study

8.10 Duration of the Study

For an individual patient, the maximum duration of the study will be up to 99 days, including up to 48 hours for screening, 6 days' treatment and follow-up at 3 months (D90 with a ±7-day window).

The study will close when all patients have completed the 3-month follow-up visit.

8.11 Premature Termination of the Study

The Sponsor reserves the right to stop the study at any time on the basis of new information regarding safety or efficacy (e.g., discovery of an unexpected, significant or unacceptable risk to the patients enrolled in the study), or if study progress is unsatisfactory (e.g., failure to enrol patients at an acceptable rate), or for other valid reasons (e.g., Sponsor decides to suspend or discontinue development of the drug). After such a decision is made, the Investigator must inform all on-study patients within 1 week. All delivered study materials must be collected and all e-CRF pages completed to the extent possible.

8.12 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of their research team must not disclose any information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be identified on the e-CRF and other documents submitted to the Sponsor/CRO by their study subject number, not by name. Documents that identify the subject must not to be submitted to the Sponsor/CRO (e.g. the ICD) and must be maintained in confidence by the Investigator. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that subject confidentiality is protected.

8.13 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties – regulatory authorities, Investigators and IEC/ IRB.

A significant safety issue is one that has a significant impact on the course of the clinical study or programme (including the potential for suspension of the development programme or amendments to protocols) or warrants immediate update of informed consent.

8.14 Publication Policy

Any manuscript, abstract or other publication or presentation of results or information arising in connection with the study (including any ancillary study involving study subjects) must be submitted to the Sponsor for review and comment at least 14 days prior to submission for publication or presentation. No single centre or groups of centres may publish individually without review and approval from the trial Steering Committee. The Sponsor's comments on the proposed publication shall be considered in good faith by the authors. The Sponsor may delay such submission by a maximum of 90 days if it reasonably believes that publication of results may compromise its intellectual property rights or may insist that such information or data is removed from the proposed

publication. Publication of the results will not include confidential information without the permission of the Sponsor.

The original eCRF pages and all data generated during the study under this protocol will become the property of the Sponsor.

The Sponsor may announce quality-assured summary data in order to comply with the requirements of financial regulatory authorities, while ensuring so far as possible that such announcements will not compromise the Investigators' ability to publish the data in appropriate scientific forums. Authorship of communications arising from the trial-related data and subsequent analysis may include members from the contributing site(s) including basic research laboratories and Sponsor's personnel.

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