inflaRx

CONFIDENTIAL

CLINICAL STUDY PROTOCOL

A PRAGMATIC ADAPTIVE RANDOMIZED CONTROLLED PHASE II/III MULTICENTER STUDY OF IFX-1 IN PATIENTS WITH SEVERE COVID-19 PNEUMONIA –– "PANAMO"

Protocol Number:	IFX-1-P2.9
Compound:	IFX-1
Phase:	II -III
Indication:	Severe pneumonia in context of COVID-19
EudraCT Number:	2020-001335-28
Sponsor Name and Address:	InflaRx GmbH Winzerlaer Strasse 2 07745 Jena, Germany
Version and Date:	Version 2.0, 30 July 2020

PROTOCOL SIGNATURES

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Protocol Number:	IFX-1-P2.9
Title:	A pragmatic adaptive randomized controlled phase II/III multicenter study of IFX-1 in patients with severe COVID-19 pneumonia --- "PANAMO"

Sponsor Signatory:

_____ _____

Date

Medical monitor name and contact information will be provided separately.

Statistician:

_____ _____

Date

Signature of Coordinating Investigator

Protocol Number: IFX-1-P2.9

Title: A pragmatic adaptive randomized controlled phase II/III multicenter study of IFX-1 in patients with severe COVID-19 pneumonia --- "PANAMO"

Herewith I declare that I have read and understood the present protocol and agree to honor each part of it. By signing this study protocol, I agree to conduct the clinical study, following approval by an Ethics Committee, in accordance with the study protocol, the current International Council for Harmonization Guidelines for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all the subjects enrolled in the study by my site will be treated, observed, and documented in accordance with this protocol. I will ensure that all persons assisting with the study under my supervision are adequately informed about the protocol, the investigational product, and their duties.

_____ _____

Alexander Vlaar, MD, PhD Date
Coordinating Investigator

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ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	anti-drug antibody
ADL	Activities of Daily Living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AMC	Amsterdam Medical Center
AST	aspartate aminotransferase
BSC	best supportive care
BDB	Beijing Deferengui Biotech
C5a	complement factor 5a
CFR	Code of Federal Regulations
CI	confidence interval
CIF	cumulative incidence function
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease-19
CRO	Contract Research Organization
CT	computed tomography
EC	Expert Committee
eCRF	electronic case report form
ECG	Electrocardiogram
ECMO	extracorporeal membrane oxygenation
EU	European Union
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EOS	end of study
EQ-5D	EuroQol 5-D
FSH	follicle stimulating hormone
FUV	follow-up visit
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HRT	hormone replacement therapy
HS	hidradenitis suppurativa
IB	Investigator Brochure

IEC	Independent Ethic Committee
ICH	International Council for Harmonisation
ICF	informed consent form
ICU	intensive care unit
IgG4	immunoglobulin G4
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
iDMC	independent Clinical Trial Data Monitoring Committee
iSMB	Independent Safety Monitoring Board
IV	intravenous
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MRI	magnetic resonance imaging
NIH	National Institutes of Health
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PaO_2 / FiO_2	oxygenation index
PCR	polymerase chain reaction
PD	pharmacodynamic
PE	pulmonary embolism
PK	pharmacokinetic
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SoA	Schedule of Assessments
SOC	standard of care
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
VTE	venous thromboembolism
WHO	World Health Organization
WOCBP	women of childbearing potential

1. SYNOPSIS

Title of Study:

A PRAGMATIC ADAPTIVE RANDOMIZED, CONTROLLED PHASE II/III MULTICENTER STUDY OF IFX-1 IN PATIENTS WITH SEVERE COVID-19 PNEUMONIA --- "PANAMO"

Protocol/Study Number: IFX-1-P2.9

EudraCT Number: 2020-001335-28

Type of Study:	**Indication:**
Phase II/III Study	Severe pneumonia in context of Coronavirus Disease-19 (COVID-19)

Sponsor: InflaRx GmbH, Winzerlaer Strasse 2, 07745 Jena, Germany

Coordinating Investigator: Alexander Vlaar, MD, PhD, Amsterdam UMC

Study Site(s):

Approximately 25 sites in approximately 7 countries in West and East Europe, United States (US), and Latin America

Phase of Development: II/III

Objectives:

Primary Objectives:

Phase II: To explore the effect of IFX-1 on COVID-19 related severe pneumonia (hypothesis generating)

Phase III: To demonstrate the efficacy of IFX-1 to improve survival outcomes of severe COVID-19 pneumonia (confirmative)

Secondary Objectives:

Phase II and Phase III

- To assess and define other parameters of efficacy
- To assess the safety of IFX-1

Methodology:

This is a pragmatic, adaptive, randomized, multicenter phase II/III study evaluating IFX-1 for the treatment of COVID-19 related severe pneumonia. The study consists of two parts: Phase II, an open-label, randomized, 2-arm phase evaluating best supportive care (BSC) + IFX-1 (Arm A) and BSC alone (Arm B); and Phase III, a double-blind, placebo-controlled, randomized phase comparing standard of care (SOC) + IFX-1 (Arm A) versus SOC + placebo-to-match (Arm B). The SOC includes venous thromboembolism prophylaxis at a minimum, and may include other international and country-specific recommended treatments for COVID-19 per the locally adopted treatment recommendations.

At the time of writing of Protocol Version 2.0, Phase II of the study has been completed and 30 patients have been treated. A preliminary interim analysis has been performed to assess the clinical benefit of the treatment using the assessed clinical parameters. An expert committee has monitored safety and the supported re-definition of relevant clinical endpoint(s) for Phase III.

In Phase II, patients in Arm A were treated with a maximum of 7 intravenous (IV) doses of IFX-1 800 mg over a period of 29 days. The first 5 treatments at days 1, 2, 4, 8, and 15 were administered to all patients. Treatment at day 22 was only administered in the event that a patient had not been extubated and discharged from the intensive care unit (ICU). In case a patient's clinical situation worsened after day 8, although an initial clinical benefit was observed, one additional administration of 800 mg IFX-1 between day 11 and 13 could have been given at investigator discretion. Loss of clinical benefit could, in this situation, relate to the exceptionally high complement factor 5a (C5a) levels observed in some cases of COVID-19 related pneumonia and associated shortened IFX-1 half-life.

Phase III of the study follows a group-sequential design (two stages) with one interim analysis for stopping for futility or stopping for efficacy. A total of 180 patients will be randomized into Arm A and Arm B using a 1:1 allocation ratio for the first stage; based on results of the interim analysis, up to an additional 180 patients will be randomized using the same allocation ratio for the second stage.

In Phase III, patients will be treated with a maximum of 6 IV doses of IFX-1 800 mg (Arm A) or placebo (Arm B) at days 1, 2, 4, 8, 15, and 22, as long as the patient is still in the hospital (even if discharged from the ICU).

If possible, patients will be assessed for quality of life using the EuroQol-5D (EQ-5D).

Patients will be followed for survival and their clinical status assessed by the Glasgow Outcome Scale.

Number of Patients:

Phase II: 30 patients (15 arm A+ 15 arm B)

Phase III: Total of 180 patients (approximately 90 per arm) in Stage 1 and 180 patients (approximately 90 per arm) in Stage 2. Simulations to evaluate the statistical properties of the group-sequential design yielded an overall 90% power to show superiority of IFX-1 for the primary endpoint of all-cause mortality. The simulations were based on the assumption that IFX-1 can reduce a 30% mortality under SOC by 50% to a mortality of 15%.

Study Population:

Study patients are enrolled into the study using a deferred consent procedure or another legally acceptable local consent procedure in this special ICU situation.

Phase II

Key inclusion criteria for Phase II of the study included the following: patients must have been at least 18 years of age or older with clinically evident or otherwise confirmed severe

pneumonia, oxygenation index (PaO_2 / FiO_2) at time of enrollment of ≤ 250 and ≥ 100, and had Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection confirmation at screening and at enrollment.

Key exclusion criteria for Phase II of the study included the following: PaO_2 / FiO_2 ≤ 99 or ≥ 250 at screening, intubated > 48h at time of enrollment, demonstrated an improvement in past 24h prior to enrollment in oxygenation and ventilation/support parameters, known history of chronic dialysis or received renal replacement therapy in past 14 days, and history of chronic obstructive pulmonary disease (COPD).

All inclusion and exclusion criteria are listed for Phase II in Section 6.1.

Phase III

Patients must meet all the following criteria at randomization to be enrolled into Phase III of the study:

1. At least 18 years of age or older
2. Patient on invasive mechanical ventilation (but not more than 48h post intubation at time point of randomization)
3. Patients with a PaO_2 / FiO_2 ratio of < 200 and > 60 at randomization (one representative measurement within 6h before randomization)
4. SARS-CoV-2 infection confirmation (tested positive in last 14 days before randomization with locally available test system)

Patients who fulfill any of the following criteria at randomization are not eligible to participate in Phase III of the study:

1. Intubated > 48h at time point of randomization
2. Expected stop of invasive ventilation or expected extubation in the next 24h without additional intervention according to judgment of the investigator
3. Known history of chronic dialysis OR received renal replacement therapy in past 14 days OR anticipated to receive renal replacement therapy within 24h after randomization
4. Known history of progressed COPD as evidenced by use of daily maintenance treatment with long-acting bronchodilators or inhaled/oral corticosteroids for > 2 months
5. Treatment of COVID-19 with investigational antibody treatment(s) which are not approved or not included in locally adopted treatment guidelines (e.g., World Health Organization [WHO] guidance, National Institutes of Health [NIH] COVID-19 treatment guidelines) for this indication in the past 7 days (Note: Antibody treatment[s] given within past 7 days for pre-existing diseases, other than COVID-19, are allowed.)
6. At time point of randomization, treatment of COVID-19 with investigational treatments which are not approved or not included in locally adopted treatment guidelines for this indication (e.g., WHO guidance, NIH COVID-19 treatment guidelines), including SARS-CoV-2 multiplication inhibitor(s) or immunomodulator(s). (Note: If a locally adopted treatment guideline recommends drugs such as remdesivir, dexamethasone, or anticoagulation, this would be allowed. Adopted guidelines and updates must be documented at study initiation and throughout the conduct of the study.)

7. Received cytokine adsorption therapy in past 3 days
8. Known hypersensitivity to IFX-1 or any other ingredient of the study medication
9. Serum or urine pregnancy test positive before randomization (required for women of childbearing potential)
10. Received organ or bone marrow transplantation in past 3 months
11. Known cardio-pulmonary mechanical resuscitation in past 14 days
12. Patient moribund or expected to die in next 24h according to the judgment of the investigator
13. Known to have received anti-cancer therapy for hemato-oncological disease in past 4 weeks OR known to have active malignant disease at time point of randomization
14. Known severe congestive heart failure (New York Heart Association [NYHA] Class III-IV; see Appendix 8)
15. Known history of chronic liver disease (Child-Pugh B or C; see Appendix 9)
16. Participating in or has participated in other investigational interventional studies (drug or device) within the last 7 days before randomization

Test Product, Dose, and Mode of Administration:

Phase II

In Arm A, patients received BSC + IFX-1. IFX-1 was to be administered as a 30-60 minute IV infusion as follows: 800 mg on days 1, 2, 4, 8, and 15 and, if not extubated or in weaning process in case of tracheostomy, may have received an additional 800 mg dose at day 22. IFX-1 treatment was to be ceased if signs of unacceptable toxicity or intolerability occurred. In case a patient's clinical situation worsened after day 8, although an initial clinical benefit was observed, one additional administration of 800 mg IFX-1 between day 11 and 13 may have been given at investigator discretion.

Phase III

In Arm A, patients will receive SOC + IFX-1. IFX-1 will be administered as a 30-60 minute IV infusion as follows: 800 mg at days 1, 2, 4, 8, 15, and 22, as long as the patient is still in the hospital (even if discharged from the ICU). IFX-1 treatment shall be ceased if signs of unacceptable toxicity or intolerability occur.

Reference Therapy, Dose, and Mode of Administration:

Phase II

In Arm B, patients received BSC alone.

Phase III

In Arm B, patients will receive SOC + Placebo in the same schedule as described for Arm A.

Expected Study Duration:

First patient first visit = March 2020 (Phase II)

Last patient last follow-up visit = May 2021 (Phase III)

Criteria for Evaluation

Phase II

Primary Endpoint:

The primary endpoint was the relative change (%) from baseline (day 1 prior to study drug administration at ± 1h of randomization) in oxygenation index (PaO_2 / FiO_2) in supine position at day 5.

Secondary endpoints included the number of patients (%) achieving an early and late response, relative change (%) from baseline (day 1 prior to study drug administration at ± 1h of randomization) in PaO_2 / FiO_2 in supine position at day 3, 7, 9, and 11, all cause 28-day mortality (%), and frequency, severity, and relatedness to study drug of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Further details on secondary and other endpoints for Phase II are provided in Section 4.2.1.

Phase III

Primary Endpoint:

- 28-day all-cause mortality

Secondary Endpoints:

- Proportion of patients free of any renal replacement therapy within 28 days upon randomization
- Proportion of patients developing acute kidney failure (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73m², assessed by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) during ICU stay and at day 28
- Proportion of patients with an improvement in the 8-point ordinal scale (Appendix 7) (day 15, day 28)
- Frequency, severity, and relatedness to study drug of serious and non-serious TEAEs

Other Endpoints:

- Time to first extubation
- 60-day mortality
- Glasgow Outcome Scale score assessed at study day 60
- Quality of life assessed by EQ-5D at study day 60

Statistical Methods:

Phase II

For efficacy analyses, the relative change (%) from baseline (day 1 prior to study drug administration at ± 1h of randomization) in oxygenation index (PaO_2 / FiO_2) in supine position at day 3, 5, 9, and 15 was to be analyzed with a linear repeated measures model with post-baseline time points as outcome variables and baseline value as an explanatory variable. Least square mean differences between treatment arms and their 95% confidence interval (CI) were to be calculated and displayed for each time point separately (day 3, 5, 9 and 15), with the evaluation at day 5 reflecting the primary endpoint. Early response, late response, and reaching ICU discharge alive were to be analyzed as three separate time-to-event variables. All-cause mortality was to be analyzed as a censored time-to-event variable with Kaplan-Meier methods. Laboratory endpoints were to be analyzed descriptively by time point and treatment arm. Glasgow Outcome Scale was to be analyzed by ordinal regression analysis.

For safety analyses, the occurrence of adverse events (AEs) was to be compared between treatment arms. The number and percentage of patients with SAEs was to be analyzed.

Further details of statistical methods for Phase II are provided in Section 10.1.

Phase III

Efficacy:

All efficacy analyses will be performed based on all randomized patients according to the intention-to-treat principle.

The statistical study design of Phase III is a group-sequential adaptive design (two stages) with one interim analysis for stopping for futility or stopping for efficacy. The primary efficacy variable is 28-day mortality (proportion of patients deceased until day 28).

A total of 180 patients (approximately 90 per arm) will be randomized in Stage 1 and up to 180 patients (approximately 90 per arm) in Stage 2. This results in 90% overall power (90% probability to either show efficacy after Stage 1 or Stage 2). The power calculation is based on an overall 2.5% one-sided alpha, Pocock's approach to account for the group-sequential design, a binding futility stop if the z-statistic is 0 or lower after the first stage and an assumed 30% 28-day mortality under Placebo and 15% 28-day mortality under IFX-1 treatment.

A total of 180 patients will be randomized to Arm A and Arm B using a 1:1 allocation ratio for the first stage. The interim analysis is performed after all 180 patients have been followed-up until day 28 (or died before). In case the interim analysis does not result in an early stop for efficacy or futility, 180 additional patients will be randomized in a ratio of 1:1 into Arm A and B. The maximum number of patients in the study will not exceed 360.

The group sequential design to show superiority of IFX-1 + SOC compared to SOC alone will make use of a one-sided alpha level of 2.5% and a binding futility stop and will test for superiority (lower mortality among IFX-1 treated patients). The primary statistical analysis will be based on a logistic regression model with outcome 28-day mortality and explanatory variables treatment arm (Arm B versus Arm A), age, sex (male versus female), and PaO_2 / FiO_2 at randomization.

The critical values for the interim and the final analysis are derived according to Pocock's design resulting in critical values of 2.176 for both stages. The z-statistic at each stage will be calculated as the proportion of the beta coefficient for the treatment arm effect and its standard error from the logistic regression model. The study will be stopped for futility if the z-statistic for the first stage is 0 or lower.

The z-statistics of the first and the second stage will be combined using the weighted inverse normal combination function (Bauer and Köhne 1994; Bauer and Köhne 1996). The weights are chosen as w_1= sqrt(180/360) and w_2= sqrt(1-w_1^2).

Secondary efficacy endpoints will only be addressed with statistical hypothesis tests if the primary endpoint is statistically significant (only after the first stage or after the second stage). Therefore, a full overall 2.5% one-sided alpha will be spent for the secondary efficacy endpoints. Multiplicity in the secondary endpoints will be addressed with the fallback method. The secondary endpoints will be evaluated using a similar logistic regression model as for the primary endpoint, where instead of the 28-day mortality (proportion of patients deceased until day 28) the following variables will be used:

1. Proportion of patients with an improvement in the provided ordinal scale at day 28 (at least one score point lower than at randomization)
2. Proportion of patients with an improvement in the provided ordinal scale at day 15 (at least one score point lower than at randomization)
3. Proportion of patients free of any renal replacement therapy within 28 days upon randomization
4. Proportion of patients developing acute kidney failure (eGFR < 15 mL/min/1.73m²) during ICU stay and at day 28

The ordering of the secondary endpoints for hypothesis testing will be as in above mentioned list. The alpha for the fallback method will be attributed to the 4 secondary endpoints in the following way: 2%, 0.2%, 0.2%, and 0.1%. If the preceding hypothesis test is not significant, subsequent tests will be performed at the aforementioned alpha level. If tests are significant, the alpha is added to the subsequent hypothesis test (e.g., if the primary hypothesis test is significant and secondary endpoints 1-3 are all significant, the fourth secondary endpoint will be tested at an alpha of 2.5%; if the third secondary endpoint is not significant, the fourth secondary endpoint will be tested at an alpha of 0.1%).

The primary endpoint as well as all secondary endpoints will also be evaluated as censored time to event variables by Kaplan-Meier type methods. All time to event endpoints will also be evaluated via proportional hazards models with the explanatory variables treatment arm (Arm B versus Arm A), age, sex (male versus female) and PaO_2 / FiO_2 at randomization.

Safety:

The occurrence of TEAEs will be compared between treatment arms. TEAEs will be analyzed according to the number and percentage of patients who had a TEAE, as well as the number of TEAEs in total. Additionally, the number and percentage of patients with TEAEs will be further grouped by severity and causal relationship. The number and percentage of patients with serious TEAEs and adverse events of special interest (AESIs) and the total number of serious TEAEs and AESIs will be analyzed. Where TEAEs are grouped by severity or

relationship, the maximum severity/relationship per patient and class of TEAE will be considered.

Interim Analysis:

The interim analysis is performed after all 180 patients in Stage 1 have been followed-up until day 28 (or died before). The study will be stopped for futility if the z-statistic of the primary efficacy analysis is 0 or lower. The study will be stopped for efficacy if the z-statistic of the primary efficacy analysis is 2.176 or higher. If the study is not stopped for efficacy or futility, another 180 patients will be randomized in Stage 2.

2. SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments: Phase II

	Screening Period	Treatment Period (Maximum 4 Weeks)													Follow-up Period (2 Months)(Telephone)	
															EOT = FUV 1	EOS= FUV 2
	Days -2 – 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 8	Day 9	Day 11	Day 13	Day 15	Day 22	Day 29/ Discharge	28 days after last IFX-1 treatment	28 days after FUV 1
Deferred Informed consent[a]	X															
Inclusion/exclusion criteria	X															
Demographics, medical/disease history, prior medications	X															
Disease/response assessments[b]	X			X		X	X		X	X	X	X	X	X		
Imaging[c]	X					X			X			X		X		
Concomitant disease	X															
Concomitant medications	X	X		X			X		X			X	X			
Blood sample for plasma complement and PK assessment[d]		X	X					X						X		
IV administration of IFX-1[e]		**X**	**X**		**X**			**X**		**(x)**		**X**	**(x)**			
Safety Assessments																
Weight	X				X			X				X	X	X		
Height	X															
Physical examination	X				X			X				X	X	X		
Safety laboratory test[f]		X	X		X			X		(x)		X	X	X		

Pregnancy test[g]	X													X		
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X												X			
Survival status								X					X	X	X	X

CT = computed tomography; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; FUV = follow-up visit; IMP = investigational medicinal product; IV = intravenous; MRI = magnetic resonance imaging; PK = pharmacokinetic

a Obtaining of informed consent was to be deferred for the ICU patients (see Section 6.3).

b Disease/response assessments included evaluation of lung function and evaluation of early and late response (see Section 8.1.2).

c Imaging was to be performed by X-ray or CT scan or MRI, per investigator decision. Once the imaging choice was made, subsequent assessments should have been made using the same modality whenever possible. Imaging either at day 29 or day of discharge ± 3 days.

d Blood samples were to be collected for measurement of plasma concentrations and C3a and C5a of IFX-1 **before administration of IMP** (see Section 8.1.4), if possible.

e The first 5 treatments of IFX-1 at day 1, 2, 4, 8, and 15 were to be administered to all patients randomized to Arm A. Treatment at day 22 was only to be administered in the event that a patient had not been extubated and discharged from ICU. In case a patient's clinical situation would worsen after day 8, although an initial clinical benefit was observed, one additional administration of IFX-1 between day 11 and 13 could have been given at investigator discretion, represented as (x) above.

f Safety laboratory tests included hematology, coagulation parameters, chemistry, urinalysis, and other screening tests (see Table 3). Blood samples for safety laboratory analysis should have been obtained after vital signs assessments were performed, but **before administration of IMP**.

g Blood samples for serum pregnancy testing were to be collected only for women of childbearing potential.

h Core body temperature, heart rate, respiratory rate, and blood pressure (diastolic and systolic) were to be assessed at each visit at pre-dose, and H0+1h, where H0 is the beginning of IFX 1 administration, on the days of IMP administration and at further time points whenever medically indicated. Vital signs were to be measured in a supine position (after a rest of at least 1h in case of position switch from prone position), preferably in the morning.

Table 2 Schedule of Assessments: Phase III

	Screening/ Randomization	Treatment Period									Follow-up Period (Telephone possible)
		Week 1			Week2	Week 3	Week 4	Week 5	Any time		FUV
	Screening not more than 24h before randomization	Day 1 (calendar day of random-ization)	Day 2	Day 4	Day 8	Day 15 (if still in hospital)	Day 22 (if still in hospital)	Day 28 (if still in hospital)	ICU discharge	Hospital discharge	Day 60 (60 +/- 3 days after randomi-zation
Deferred informed consent[a]	X										
Screening / Baseline Assessments											
Inclusion/exclusion criteria	X										
Urine analysis (dipstick)	X										
Pregnancy test[b]	X										
Weight	X										
Height	X										
PaO_2 / FiO_2[c]	X										
Demographics, COVID-19 history, SARS-CoV-2 mRNA test[d]	X										
Medical history/ concomitant disease	X										
Prior medications and procedures	X										
Intubation date	X										
Randomization											
Randomization	X										
IMP Administration											
IMP administration[e]		**X**	**X**	**X**	**X**	**X**	**X**				

	Screening/ Randomization	Treatment Period									Follow-up Period (Telephone possible)
		Week 1			Week2	Week 3	Week 4	Week 5	Any time		FUV
	Screening not more than 24h before randomization	Day 1 (calendar day of random-ization)	Day 2	Day 4	Day 8	Day 15 (if still in hospital)	Day 22 (if still in hospital)	Day 28 (if still in hospital)	ICU discharge	Hospital discharge	Day 60 (60 +/- 3 days after randomi-zation
Endpoint Assessments											
Organ support (renal replacement therapy, ECMO, mechanical ventilation)		X									
Extubation and re-intubation date(s)		X									
Ordinal scale evaluation[f]	X				X	X	X	X	X	X	
Survival status		X									X
Quality of life (EQ-5D)											X
Glasgow Outcome Scale											X
Safety Assessments											
Safety laboratory tests[g]	X	X	X	X	X	X	X	X	X	X	
Creatinine[h]	X	X	X	X	X	X	X	X	X	X	
Vital signs[i]		X	X	X	X	X	X	X	X	X	
Adverse events[j]	X	X									X
Physical examination	X	X	X	X	X	X	X				
Concomitant medications and procedures		X									
12-lead ECG	X								X		
PK/PD Assessments (Country-specific)[k]											
IFX-1 sample	X				X					X	

	Screening/ Randomization	Treatment Period									Follow-up Period (Telephone possible)
		Week 1			Week2	Week 3	Week 4	Week 5	Any time		FUV
	Screening not more than 24h before randomization	Day 1 (calendar day of random-ization)	Day 2	Day 4	Day 8	Day 15 (if still in hospital)	Day 22 (if still in hospital)	Day 28 (if still in hospital)	ICU discharge	Hospital discharge	Day 60 (60 +/- 3 days after randomi-zation
ADA sample	X									X	
C5a sample	X				X					X	

ADA = anti-drug antibody; C5a = complement factor 5a; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; EQ-5D = EuroQol 5-D; FUV = follow-up visit; IMP = investigational medicinal product; IV = intravenous; PaO_2 / FiO_2 = oxygenation index; PK/PD = pharmacokinetic/pharmacodynamic

a Obtaining of informed consent is proposed to be deferred or by any other legally acceptable local consent procedure for the ICU patients in this study (see Section 6.3).

b Serum or urine samples for pregnancy testing will be collected only for women of childbearing potential.

c PaO_2 / FiO_2 should be assessed within 6h before randomization (one representative measurement)

d SARS-CoV-2 infection confirmation will be done, if not already tested positive in last 14 days before randomization, with locally available test system

e Up to 6 treatments of IMP will be administered at days 1, 2, 4, 8, 15, and 22, as long as the patient is still in the hospital, even if discharged from the ICU.

f Ordinal scale score will be documented at the visits indicated, including the date (one value per assessment day, that best represents the patient's condition at that day)

g Safety laboratory tests include hematology (hemoglobin, hematocrit, platelet count, red blood cell count, red blood cells (MCV), white blood cell count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils), coagulation parameters (aPTT, PT, D-dimer), blood chemistry (ALT, AST, LDH, total bilirubin, and CRP) (see Appendix 1, Table 4). Blood samples for safety laboratory analysis should be obtained at indicated days during routine sampling (one representative value, if taken more than once a day).

h Creatinine assessment should be obtained at indicated days during routine sampling (one representative value, if taken more than once a day).

i Vital signs (core body temperature, heart rate, respiratory rate, blood pressure [diastolic and systolic]) will be assessed at indicated visits at pre-dose within 1h before administration of IMP (one representative measurement closest to IMP administration) and at further time points whenever medically indicated. Blood pressure and heart rate measurements will be assessed with an intra-arterial catheter, or a completely automated device. Manual techniques will be used only if an automated device is not available.

j Adverse event reporting will follow special considerations for the ICU setting as described in Appendix 3.

k PK/PD sampling will be conducted at sites in the US, Europe, and Russia. PK/PD samples will be taken within 1h before administration of IMP.

3. INTRODUCTION AND BACKGROUND INFORMATION

3.1. Background

There are daily increasing numbers of Severe Acute Respiratory Syndrome (SARS) Coronavirus 2 (SARS-CoV-2) infected individuals globally and reports on impact / mortality vary constantly. As of 23 July 2020, over 15 million documented cases were reported worldwide of which more than 619,000 died (World Health Organization [WHO] 2020). Clinical manifestations of Coronavirus Disease-19 (COVID-19) vary, with approximately 5% of patients having critical manifestations (such as respiratory failure, septic shock, and/or multiple organ dysfunction) and 17-35% of hospitalized patients being treated in an intensive care unit (ICU), of whom 29-91% require invasive mechanical ventilation (Wiersinga et al. 2020).

The main COVID-19 characterizing clinical features are age greater than 50 years and presence of comorbidities such as hypertension and diabetes, whereas main laboratory findings show hepatic and renal dysfunction in the presence of leukopenia, lymphopenia, increase of D-dimers, and strong inflammatory cytokine activation (Guan et al. 2020; Huang et al. 2020; Liu et al. 2020; Garg et al. 2020; Wiersinga et al. 2020). Elevated D-dimer values have been shown to be strongly associated with poorer prognosis. It is also reported that the complement cascade is highly activated (Gao et al. 2020). One hallmark of progressed disease in patients who become severely diseased is the association of blood neutrophil increases with the disease severity, and neutrophil infiltration in the heart and liver.

Monoclonal antibodies directed against key inflammatory mediators, such as interleukin 1 and 6 and complement factor 5a (C5a), aim to modulate the overwhelming inflammatory response following SARS-CoV-2 infection, thereby preventing organ damage (Wiersinga et al. 2020). These targeted immunomodulatory agents are currently being evaluated for the management of COVID-19 and may prevent disease progression in hospitalized patients.

3.2. Study Rationale

3.2.1. Drug Profile

IFX-1 is a chimeric immunoglobulin G4 (IgG4) monoclonal anti-human C5a antibody, which specifically binds to the soluble human complement split product C5a. IFX-1 has been demonstrated to block C5a-mediated biological effects with high efficacy in vitro. C5a is one of the most potent inflammatory factors, triggering innate immune responses and bridging to adaptive immune responses (Dunkelberger and Song 2010). In blood, C5 is cleaved to C5a by components of the classical and alternative complement pathway, and the coagulation pathway, whereas in tissue, factors of the alternative complement and the coagulation pathway factors play a major role in C5a generation (Hess and Kemper 2016).

3.2.2. Non-clinical and Therapeutic Studies

Non-clinical studies were conducted to assess pharmacological and toxicological aspects of IFX-1 and showed that IFX-1 was able to rapidly bind to its target, the human C5a, and achieve an almost complete blockade of C5a-induced biological effects. At the same time, cleavage of C5 and formation of the complement membrane attack complex was not disrupted in vitro.

IFX-1 did not demonstrate any cross-reactivity or bioactivity in species other than humans and non-human primates (Section 4.2 of the Investigator Brochure [IB]). Therefore, toxicology studies were only conducted in cynomolgus monkeys.

IFX-1 has been investigated in viral induced lung injury in monkeys infected with the avian flu virus H7N9. It had been shown that the neutrophil influx into the lung as well as the lung damage could be greatly reduced by this therapeutic attempt. In addition, the viral replication was greatly reduced as well, which is believed to be an indirect effect (Sun et al. 2015). This research was in line with findings generated in an H5N1 model of disease in rodents (Sun et al. 2013). Since then, the role of complement and specifically C5a for viral induced lung injury has become an accepted concept in basic research (Wang et al. 2015). The same research group then confirmed the role of the C5a/C5a-receptor signaling axis for viral replication, for lung neutrophil influx and damage in a mouse model of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (Jiang et al. 2018). Another group of researchers then confirmed the role of complement activation and made similar findings on viral replication inhibition and lung damage reduction in complement deficient mice in a SARS virus infection model (Gralinski et al. 2018). One finding of this study was that complement deficient mice (C3-/-) had significantly less infiltration of the lungs with neutrophils and monocytes, also confirming earlier findings in greater detail for SARS-CoV induced viral lung injury.

This body of research has led to the approval by the Chinese FDA of two ongoing trials in SARS-CoV-2 infected patients in China with the monoclonal anti-C5a antibody BDB-1 (S-FDA approval number 2020L00003). BDB-1 is generated from the InflaRx IFX-1 cell line which has been transferred and licensed to the InflaRx collaborator Beijing Deferengui Biotech Co. (BDB). BDB develops BDB-1 under their responsibility in China and InflaRx has all rights to any discoveries made by BDB-1 globally outside China, where InflaRx develops IFX-1 in the rest of the world. The BDB-1 trials are ongoing, however data of the first two open label treated patients were reported in context of a research article by Gao et al. 2020 (see Section 3.2.4).

None of the Good Laboratory Practice-compliant studies in cynomolgus monkeys revealed relevant toxicological or safety concerns for IFX-1. During single-dose and repeat-dose administration of IFX-1 at doses of up to 50 mg/kg body weight in cynomolgus monkeys no direct IFX-1-related toxicological or adverse findings within an extended core battery of safety pharmacology assessments were observed. Results showed dose-related increases in systemic and maximum exposure in the investigated dose range of 1 to 50 mg/kg body weight. Anti-drug

antibodies (ADAs) were detected in 1 animal in the 26-week repeat-dose study. This animal died, most likely because of an ADA-mediated immune complex formation.

An overview of the non-clinical toxicology studies that were conducted with IFX-1 is available in Table 8 of the IB.

For further details, refer to Section 4 of the IB.

3.2.3. Experience in Humans

At the time of writing of Protocol Version 2.0, Phase II of the current study has been completed and all 30 enrolled patients have been treated (15 in Arm A [best supportive care (BSC) + IFX-1] and 15 in Arm B [BSC alone]) for up to 28 days. Relative change (%) from baseline to day 5 in oxygenation index was assessed as the primary endpoint along with additional clinical parameters until day 28. Relative change in the oxygenation index at day 5 showed no differences between treatment groups. However, IFX-1 treatment was associated with a lower 28-day all-cause mortality when compared to the BSC arm, along with trends in disease improvement, as evidenced by fewer patients experiencing renal impairment assessed by estimated glomerular filtration rates (eGFR), more patients showing reversal of blood lymphocytopenia and a greater lowering of lactate dehydrogenase concentrations. In IFX-1-treated patients, pulmonary embolisms (PE) reported as serious adverse events (SAEs) were lower compared to the BSC arm. Also, a temporary increase of D-dimer levels, as potential expression of induction of blood clot lysis, was detected in the first days after initiation of IFX-1 treatment.

Over a treatment period of 28 days, patients in the IFX-1 arm received a maximum of 7 doses of 800 mg IFX-1 intravenously (IV) on separate days. At randomization, 18 patients (60%) were intubated, and 12 patients (40%) had other oxygen supply. A higher number of patients with 2 or more comorbidities associated with increased COVID-19 mortality were reported in the IFX-1 treatment arm compared to the BSC arm. Twenty-eight-day all-cause mortality in the IFX-1 treatment arm was 13% (2 out of 15) versus 27% (4 out of 15) in the BSC arm. In the BSC arm, 4 patients died of COVID-19-induced multi-organ failure, and 3 of them had PE reported as SAEs. In the IFX-1 arm, one patient died after an acute ventilator tube complication (leakage) and one patient with a history of severe chronic obstructive pulmonary disease died of pulmonary failure. Serious AE rates were comparable between groups, but the rate of PE reported as SAEs was substantially lower in the IFX-1 treatment group. Upon review of the safety data, the independent data safety monitoring board has recommended continuation of the trial into Phase III.

IFX-1 is also being developed for the treatment of other inflammatory diseases. Five clinical studies in humans have been completed so far. One Phase I study in healthy volunteers (Study IFX-1-P1.1) and 4 Phase II studies: 1 in patients with early septic organ dysfunction (Study IFX-1-P2.1), 1 in patients undergoing complex cardiac surgery (Study IFX-1-P2.2), and

2 in patients with hidradenitis suppurativa (HS) (Studies IFX-1-P2.3 and IFX-1-P2.4; Section 5 of the IB).

To date, 391 subjects (26 healthy volunteers and 365 patients) have been treated in completed clinical studies of these other inflammatory diseases, of which 294 have received IFX-1 and 92 have received placebo. IFX-1 was safe and well tolerated, with no dose relationship in the safety findings. No specific adverse reactions emerged in clinical studies of single or multiple doses IFX-1 in healthy volunteers or patients with cardiac disease, sepsis, or HS.

Currently, 4 further Phase II studies are ongoing: 1 in patients with HS (Study IFX-1-P2.4; in final analyses), 2 in patients with granulomatosis with polyangiitis and microscopic polyangiitis (also referred to as anti-neutrophil cytoplasmic antibody-associated vasculitis; Study IFX-1-P2.5 and IFX-1-P2.6), and 1 in patients with pyoderma gangrenous (Study IFX-1-P2.7).

Data are available from the interim analysis of the main period of the Phase II Study IFX-1-P2.4 in HS, where 141 patients were treated with IFX-1 in 4 different IFX-1 dose cohorts (400 mg and 800 mg every 4 weeks, 800 mg bi-weekly, and 1200 mg every 2 weeks) and 36 patients were treated with placebo. The total treatment duration in this study, which recently completed treatment, was 9 months. Treatment with IFX-1 was safe and well tolerated with rare occurrence of adverse events (AEs) of special interest (AESIs), defined as infusion reactions, including hypersensitivity or anaphylaxis, meningitis, meningococcal sepsis, and invasive infection. Four patients experienced AEs suggestive of hypersensitivity. The reactions were moderate, and treatment continued if necessary with adequate prophylactic medication. Anti-drug antibodies during treatment were observed in a range of 5.6% to 12.9% with a trend towards increasing frequency with low dose and larger administration intervals.

3.2.4. Scientific Rationale for the Study

Neutrophil driven tissue and organ damage is known to play an important role in a wide array of acute inflammatory diseases. The mechanism leading to damage has been largely attributed to two mechanisms: 1) the release of granular enzymes and 2) the generation of so-called reactive oxygen species in which O_2 radical formation elicits a damaging effect.

One of the strongest chemoattractant substances, which is also capable of inducing both mechanisms described above is the human complement split product C5a.

Earlier research by InflaRx has demonstrated that the anti-human C5a antibody IFX-1 could significantly reduce the neutrophil and macrophage infiltration in a model of viral (H7N9) induced lung injury in monkeys (Sun et al. 2015). This was accompanied by a significantly reduced tissue damage in the lung of infected animals and also a significantly reduced viral replication when compared to mock-treated animals. The mechanism was then confirmed in a model of MERS–CoV induced lung injury where similar findings were made by using an anti-C5a receptor antibody (Jiang et al. 2018) and in a model of SARS-CoV induced lung injury by using complement C3 knockout mice (Gralinski et al. 2018). The latter study also provided

evidence for a profound complement activation in SARS virus infections in animals. These studies all suggested a role of neutrophil driven lung damage, which was induced by generation of C5a in different viral-lung injury models, including SARS viruses.

Latest data from a collaborating research group in China demonstrated strongly and significantly elevated C5a levels in severely diseased COVID-19 patients when compared to mildly diseased patients (Gao et al. 2020; Carvelli et al. 2020) and revealed evidence for a strong complement pathway driven activation of C5a in this disease. In addition, data from the first two severely diseased COVID-19 patients treated with the IFX-1 cell line derived anti-C5a antibody BDB-1, which InflaRx licensed to a collaborator in China, demonstrated clinical improvement in oxygenation index, fever reduction, and laboratory parameter normalization including liver enzymes and lymphocyte counts.

From a clinical perspective, various papers have confirmed that COVID-19 infected non-surviving patients demonstrated lung failure with close to 100% (Zhou et al. 2020) and that, in contrast to surviving patients, non-survivors demonstrated elevated white blood cell counts and neutrophils above the normal range (Wang et al. 2020; Gong et al. 2020).

In summary, there is evidence that in COVID-19 patients who are severely affected, C5a activation occurs to a large extent and that neutrophil count elevation in blood is associated with bad outcome. These human data fit well to the scientific rationale developed in animal models of viral-induced lung injury that activated neutrophils attracted to the lung may cause viral-induced lung damage. First treatment attempts with the anti-C5a antibody technology developed by InflaRx (BDB-1) in severely affected COVID-19 patients provide further evidence for the scientific rationale.

The completed Phase II portion of the current trial was exploratory in nature and was not powered to show statistically significant differences in clinical endpoints. Relative change (%) from baseline to day 5 in the oxygenation index, chosen as the primary endpoint for Phase II, showed a large variability and dependency on patient positioning and intubation status which excluded this endpoint from being used in a confirmatory study. Phase III of the study is an adequately powered, placebo-controlled, double blinded phase evaluating standard of care (SOC) + IFX-1 versus SOC + placebo-to-match with 28-day all-cause mortality as the primary endpoint, an accepted regulatory primary endpoint for critical care studies.

At the time that Phase II of this study was initiated, there was no SOC established for this newly identified disease. The SOC to be utilized in Phase III of this study reflects the current understanding of the SOC for hospitalized patients with COVID-19, which includes venous thromboembolism (VTE) prophylaxis at a minimum, and may include other international and country-specific recommended treatments for COVID-19 per the locally adopted treatment recommendations.

3.2.5. Justification for Dose

The aim for determining the dose and administration frequency for IFX-1 is to establish a pragmatic administration schedule for the COVID-19 patient population. IFX-1 dose and administration schedule was chosen based on prior pharmacokinetic (PK)/pharmacodynamic (PD) observations for IFX-1 trough values and blood C5a levels, dose-response assessment in Study IFX-1 P2.4 in HS, and the described unprecedented high C5a levels in patients with severe COVID-19 related pneumonia (Gao et al. 2020; Carvelli et al. 2020). In a population PK/PD modelling study for IFX-1 based on the data of the 2 trials in HS patients, a reduction in C5a concentration was found to be dependent on all measures of drug exposure, with increasing exposure predicting a greater reduction in C5a.

The observed half-life of IFX-1 with a single dose of 800 mg was 3 to 4 days in Study IFX-1 P2.2 in patients undergoing complex cardiac surgery. Thus, an additional dose of 800 mg at Day 4, followed by weekly administration of 800 mg IFX-1 was chosen for Study IFX-1 P2.3 in patients with HS.

In Study IFX-1 P2.3 in patients with HS, 800 mg once-weekly IFX-1 was administered for up to 9 times including an additional dose of 800 mg at Day 4. This administration schedule resulted in IFX-1 trough concentrations of around 50 µg/mL and a decrease of elevated baseline C5a levels to approximately detection limit throughout the treatment duration in the majority of patients. This dosing regimen was well tolerated, with no new safety signals, and clinical improvement of HS was observed in some patients.

In another clinical study in HS (Study IFX-1 P2.4), 4 different dosing schedules were explored, of which the highest dose was 1200 mg every 2 weeks. Safety findings were similar in all dose groups, and similar to safety findings in previous studies, with no new specific AESIs.

Based on the above data, the dosing schedule of IFX-1 for this study includes an additional dose of 800 mg IFX-1 at day 2 in the established fractionated loading dose scheme, that foresees administration of 800 mg at days 1, 4, and 8. This additional dose has been chosen due to the reported high C5a levels in COVID-19 patients (Gao et al. 2020). Therefore, the entire dosing scheme contains up to 6 IFX-1 doses of 800 mg at days 1, 2, 4, 8, 15, and 22 (or less until hospital discharge). This regimen had been employed in Phase II of this study, leading to a lower death rate and supporting efficacy signals without any new signals of unknown toxicities (Vlaar et al 2020).

3.3. Benefit/Risk Assessment

IFX-1 is a chimeric IgG4 antibody that has the potential to elicit infusion reactions, including hypersensitivity or anaphylaxis. In animal studies, one unexplained death of a cynomolgus monkey retrospectively showed development of anti-IFX-1 antibodies. In clinical studies, few patients tested positive for anti-IFX-1 antibodies, and only mild to moderate signs of hypersensitivity reactions were occasionally observed so far (overall ADA rate in the range of

5% to 13%). In total, IFX-1 showed very good tolerability in clinical studies. The majority of observed AEs were attributed to the underlying diseases and IFX-1 AESIs occurred occasionally (see IB for details).

A summarized in Section 3.2.4, there is evidence that in COVID-19 patients who are severely affected, C5a activation occurs to a large extent and that neutrophil count elevation in blood is associated with worse outcomes.

Data from the interim analysis from the completed Phase II of the current study demonstrated that IFX-1 treatment was associated with a lower 28-day all-cause mortality when compared to the BSC arm, along with trends in disease improvement, as evidenced by fewer patients experiencing renal impairment, more patients showing reversal of blood lymphocytopenia, and a greater lowering of lactate dehydrogenase concentrations. In IFX-1-treated patients, PE reported as SAEs were lower compared to the BSC arm. Also, a temporary increase of D-dimer levels, as potential expression of induction of blood clot lysis, was detected in the first days after initiation of IFX-1 treatment.

Overall, the expected clinical benefit for patients suffering from COVID-19-related severe pneumonia outweighs the risks in relation to the mild to moderate side effects that have been attributed to IFX-1 so far.

4. OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objectives

The primary objective of Phase II was:

- To explore the effect of IFX-1 on COVID-19 related severe pneumonia (hypothesis generating)

The primary objective of Phase III is:

- To demonstrate the efficacy of IFX-1 to improve survival outcomes of severe COVID-19 pneumonia (confirmative)

4.1.2. Secondary Objectives

The secondary objectives of Phase II and Phase III are:

- To assess and define other parameters of efficacy
- To assess the safety of IFX-1

4.2. Study Endpoints

4.2.1. Phase II

4.2.1.1. Primary Endpoint

The primary endpoint in Phase II was the relative change (%) from baseline (day 1 prior to study drug administration at ± 1h of randomization) in oxygenation index (PaO_2 / FiO_2) in supine position at day 5.

4.2.1.2. Secondary Endpoints

The secondary endpoints in Phase II were:

- Number of patients (%) achieving an **Early Response** as defined as meeting ALL of the following criteria at day 7 after enrollment:
  - Patient alive and extubated OR oxygenation index ≥ 300 OR improvement of ≥ 30% from baseline
  - Temperature < 38°C in absence of fever decreasing medication of at least 4h
  - White blood cell count within normal limit of local lab quantifications
- Number of patients (%) reaching a **Late Response** as defined by either being **discharged alive** from hospital until day 28 **OR** meeting **ALL** of the following criteria at day 28 of the trial
  - Patient alive and extubated
  - Patient discharged from ICU
  - Patient free of shortness of breath (respiratory rate < 20) in absence of oxygen supply
  - Patient free of fever (< 37.6°C)
- Relative change (%) from baseline (day 1 prior to study drug administration at ± 1h of randomization) in oxygenation index (PaO_2 / FiO_2) in supine position at day 3, 7, 9, and 11.
- All cause 28-day mortality (%)
- Frequency, severity, and relatedness to study drug of treatment-emergent adverse events (TEAEs) and SAEs

4.2.1.3. Other Endpoints

The other endpoints in Phase II were:

- Change from baseline in alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
- Change from baseline in troponin I adjusted to glomerular filtration rate
- Change from baseline in creatinine

- Change from baseline in lymphocyte counts
- Change from baseline in neutrophil counts
- Change from baseline in D-dimers
- Change from baseline in Glasgow Outcome Scale
- Time to reach ICU discharge criteria as defined by ALL of the three criteria below:
  - Alive and extubated
  - No need for continued (>3h per day) non-invasive ventilation
  - Free of vasopressor and inotropic therapy
- Assessment of complement activation parameters and plasma concentrations of IFX-1

4.2.2. Phase III

4.2.2.1. Primary Endpoint

Based on the preliminary interim analysis of efficacy data from Phase II, the primary endpoint chosen for Phase III is 28-day all-cause mortality.

4.2.2.2. Secondary Endpoints

The secondary endpoints in Phase III are:

- Proportion of patients free of any renal replacement therapy within 28 days upon randomization
- Proportion of patients developing acute kidney failure (eGFR < 15 mL/min/1.73m², assessed by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) during ICU stay and at day 28
- Proportion of patients with an improvement in the 8-point ordinal scale (Appendix 7) (day 15, day 28)
- Frequency, severity, and relatedness to study drug of serious and non-serious TEAEs

4.2.2.3. Other Endpoints

The other endpoints in Phase III are:

- Time to first extubation
- 60-day mortality
- Glasgow Outcome Scale score assessed at study day 60
- Quality of life assessed by EuroQol 5-D (EQ-5D) at study day 60

5. STUDY DESIGN

5.1. Overall Design

This is a pragmatic, adaptive, randomized, multicenter phase II/III study evaluating IFX-1 for the treatment of COVID-19 related severe pneumonia. The study consists of two parts: Phase II, an open-label, randomized, 2-arm phase evaluating BSC + IFX-1 (Arm A) and BSC alone (Arm B); and Phase III, a double-blind, placebo-controlled, randomized phase evaluating SOC + IFX-1 (Arm A) and SOC + placebo-to-match (Arm B). The SOC includes VTE prophylaxis at a minimum, and may include other international and country-specific recommended treatments for COVID-19 per the locally adopted treatment recommendations. An independent safety monitoring board is established to monitor the safety in an ongoing manner for both parts of the study (see Sections 5.3 and 5.5).

At the time of writing of Protocol Version 2.0, Phase II of the study has been completed and all 30 patients have been treated (15 in Arm A [BSC + IFX-1] and 15 in Arm B [BSC alone]). A preliminary interim analysis has been performed to assess the clinical benefit of the treatment using the assessed clinical parameters. An expert committee (EC) has monitored safety and the supported re-definition of clinical endpoint(s) for Phase III.

In Phase II, patients in Arm A were treated with a maximum of 7 IV doses of IFX-1 800 mg over a period of 29 days. The first 5 treatments at days 1, 2, 4, 8, and 15 were administered to all patients randomized into Arm A. Treatment at day 22 was only administered in the event that a patient has not been extubated and discharged from ICU. In case a patient's clinical situation worsened after day 8, although an initial clinical benefit was observed, one additional administration of 800 mg IFX-1 between day 11 and 13 could have been given at investigator discretion. Loss of clinical benefit could in this situation relate to the exceptionally high C5a levels observed in some cases of COVID-19 related pneumonia and associated shortened IFX-1 half-life.

Phase III of the study follows a group-sequential design (two stages) with one interim analysis for stopping for futility or stopping for efficacy. A total of 180 patients will be randomized into Arm A and Arm B using a 1:1 allocation ratio for the first stage; based on results of the interim analysis, up to an additional 180 patients will be randomized using the same allocation ratio for the second stage.

In Phase III, patients will be treated with a maximum of 6 IV doses of IFX-1 800 mg (Arm A) or placebo (Arm B) at days 1, 2, 4, 8, 15, and 22, as long as the patient is still in the hospital (even if discharged from the ICU).

If possible, patients will be assessed for quality of life using the EQ-5D.

Patients will be followed for survival and their clinical status assessed by the Glasgow Outcome Scale.

5.1.1. Method of Treatment Assignment

In Phase II, patients were centrally assigned to a treatment arm by the Investigator via the randomization module of the electronic case report form (eCRF). The investigational medicinal product (IMP) was assigned to each patient by the investigator at the investigation site. Sites were each given a randomization block and instructed to assign the first patient to Arm A, the second patient to Arm B, etc. The site recorded the IMP assignment on the applicable eCRF, if required.

In Phase III, patients will be centrally assigned to a treatment arm by the investigator via an Interactive Web Response System (IWRS). IMP will be assigned to each patient by the IWRS.

IMP shipment to sites will be automatically triggered by the IWRS, and will be initiated, maintained, and controlled by the IWRS.

IMP is dispensed at the study visits as summarized in the schedule of assessments (SoA, Table 1 and Table 2).

5.1.2. Blinding

Phase II of the study was open-label and randomized, while Phase III will be double-blind, placebo-controlled, and randomized.

5.2. Patient Enrollment

In Phase II, patients were randomized to Group A or B. The maximum number of randomized patients in Phase II was set to 30. There was a recruitment stop after the planned number of patients for Phase II were enrolled. After the preliminary interim analysis of Phase II was performed and the EC recommended to proceed, the number of patients for Phase III was calculated according to the established hypothesis. For details on the role of the EC, see Section 5.4.

In Phase III, 180 patients will be randomized into Arm A and Arm B using a 1:1 allocation ratio for the first stage; based on results of the interim analysis, up to an additional 180 patients will be randomized using the same allocation ratio for the second stage.

5.3. Independent Safety Monitoring Board for Phase II

An independent Safety Monitoring Board (iSMB) was constituted to support safety surveillance in both treatment arms throughout Phase II and Phase III of the study. The committee included at least 2 Intensive Care specialists not involved as investigators in this study and an independent statistician.

The iSMB monitored the safety of all patients regularly, after 10, 20, and 30 patients completed their treatment in Phase II. At each review, the iSMB recommended on continuing or ending the

study. After completion of Phase II (30 patients), the iSMB has assessed the totality of available data of all patients and has recommend on proceeding to Phase III (see Section 3.2.3).

5.4. Expert Committee for Phase II

An EC was constituted to support efficacy surveillance in both treatment arms throughout Phase II of the study. The committee included the clinical study monitor and at least 3 Intensive Care specialists involved in the treatment of COVID-19 affected patients (Coordinating Investigator included).

The committee monitored the efficacy of all patients regularly, after 10, 20, and 30 patients completed their treatment. At each review, the EC was able to recommend on continuing or ending the study.

After completion of Phase II (30 patients), the EC assessed the totality of the data of all patients, taking into account the recommendations of the iSMB and recommend proceeding to Phase III, assessed appropriateness of the endpoints and scheduled assessments, and supported establishing an adequate hypothesis for Phase III.

The EC has stopped meeting at the beginning of Phase III (i.e., at the time of writing of Protocol Version 2.0).

5.5. Independent Data Safety Monitoring Board for Phase III

In Phase III, the iSMB from Phase II will continue as an independent Clinical Trial Data Monitoring Committee (iDMC). The iDMC will meet every 3 months throughout Phase III of the study to further assess safety. In addition, the iDMC will perform an unblinded assessment of the data of the interim analysis and will make recommendations on whether to continue the study or not according to the predefined early stop criteria (see Section 10.2.3.5). All available data will be provided to the iDMC before each meeting. Details will be described in a separate iDMC Charter.

5.6. Patient and Study Completion

5.6.1. Phase II

5.6.1.1. End of Treatment and Follow-up

End of treatment (EOT) was defined as last planned administration or discontinuation of IMP for other reasons. The EOT telephone visit (Follow-up Visit [FUV] 1) was to occur 28 days after last study drug administration in Phase II. The visit information obtained via the telephone call (e.g., AEs, survival status) was to be recorded.

Discontinuation of study treatment did not represent withdrawal from the study.

For details on treatment discontinuation criteria, see Section 7.2.4.

5.6.1.2. End of Study

Patients were to be followed for survival using the Glasgow Outcome Scale until the end of study (EOS) visit (FUV 2). If required, information could have been obtained by a telephone call.

The EOS for the individual patient was defined as the date of the last contact of the 2-month follow-up period, date of death, date of consent withdrawal from study participation (see Section 5.6.1.3), or the date of last contact when patients were lost to follow-up (see Section 5.6.1.4).

The entire study was to end when all patients discontinued IFX-1 AND all patients ended the study as described above.

The sponsor could have prematurely terminated Phase II of the study at any time earlier than planned for the following reasons:

- Unacceptable toxicity
- Administrative reasons

5.6.1.3. Consent Withdrawal/ Discontinuation of Study Participation

A patient could have withdrawn from Phase II of the study at any time at his/her own request without the need to provide any reason(s).

If the patient withdrew from study participation, the sponsor could have retained and continued to use any data collected before such a withdrawal of consent. However, in the case of deferred informed consent, if the consent was not obtained or if a legal representative denied the patient's participation in the study, the patient was excluded and data were no longer to be used (see Section 6.3). Patients (or legal representatives) who wished to withdraw consent/discontinue the study while still on treatment should have been encouraged by the investigator to perform the EOT visit for their own safety before any further data collection for study purposes was terminated.

If a patient withdrew from the study, he/she could have requested destruction of any samples taken and not tested, and the investigator must have documented this in the site study records.

5.6.1.4. Lost to Follow-up

A patient was to be considered lost to follow-up if he or she could not be reached after hospital discharge for scheduled contacts and the study site was unable to make contact as described below.

The following actions must have been taken if a patient could not be reached:

- The site must have attempted to re-contact the patient as soon as possible after the failed first scheduled contact.
- Before a patient was deemed lost to follow-up, the investigator or designee must have made every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts were to be documented in the patient's medical record.
- Should the patient have continued to be unreachable, he/she was considered to have been withdrawn from the study with a primary reason of lost to follow-up.

5.6.2. Phase III

5.6.2.1. End of Treatment and Follow-up

End of treatment is defined as the last planned administration or discontinuation of IMP for other reasons. The FUV is scheduled to occur 60 days after the randomization date. The visit information obtained via the telephone call (e.g., AEs, survival status) should be recorded.

Discontinuation of study treatment does not represent withdrawal from the study.

For details on treatment discontinuation criteria, see Section 7.2.4.

5.6.2.2. End of Study

The end of study for the individual patient is defined as the date of the last contact of the follow-up period (i.e., 60 days after randomization), date of death, date of consent withdrawal from study participation (see Section 5.6.2.3), or the date of last contact when patients are lost to follow-up (see Section 5.6.2.4), whatever occurs earliest.

The entire study will end when all patients have discontinued IFX-1 AND all patients ended the study as described above.

The sponsor may prematurely terminate the study at any time earlier than planned for the following reasons:

- Unacceptable toxicity
- Administrative reasons

5.6.2.3. Consent Withdrawal/Discontinuation of Study Participation

A patient may withdraw from the entire study at any time at his/her own request without the need to provide any reason(s).

If the patient withdraws from study participation, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. However, in the case of deferred informed

consent, if the consent is not obtained or if a legal representative denies the patient's participation in the study, the patient is excluded and data will no longer be used, except if local regulations would permit the use of such data in this situation (see Section 6.3). Patients (or legal representatives) who wish to withdraw consent/discontinue the study while still on treatment should be encouraged by the investigator to perform the FUV for their own safety before any further data collection for study purposes.

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

5.6.2.4. Lost to Follow-up

A patient will be considered lost to follow-up if he or she cannot be reached after hospital discharge for scheduled contacts and the study site is unable to make contact as described below.

The following actions must be taken if a patient cannot be reached:

- The site must attempt to re-contact the patient as soon as possible after the failed first scheduled contact.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Study patients are considered enrolled into the study using a deferred consent procedure or another legally acceptable local consent procedure in this special ICU situation.

6.1. Phase II

6.1.1. Inclusion Criteria

Patients must have met all the following criteria at screening and at enrollment to be randomized into Phase II of the study:

1. At least 18 years of age or older
2. Clinically evident or otherwise confirmed severe pneumonia as evidenced by at least one of the following criteria:

3. Chest X-ray or computed tomography (CT) scan or magnetic resonance imaging (MRI) with pulmonary infiltrates consistent with pneumonia
4. Clinical history in past 14 days of newly developed severe shortness of breath (> 29 breaths / minute) in the absence of oxygen supply or spontaneous peripheral oxygenation ≤ 92 with need for oxygen supply, or need for non-invasive or invasive ventilation (in conjunction with a positive test for SARS-CoV-2 infection)
5. Oxygenation index at time of enrollment (PaO_2 / FiO_2) ≤ 250 and ≥ 100 in supine position
6. SARS-CoV-2 infection confirmation (tested positive in last 14 days or test results to be obtained within 24h after enrollment, both with locally available test system).
7. No use OR stop of any corticosteroid treatment at time point of enrollment (topical treatment and systemic dose of ≤ 10mg prednisone / day equivalent allowed)

6.1.2. Exclusion Criteria

Patients who fulfilled any of the following criteria at screening were not eligible to participate in Phase II of the study:

1. Oxygenation index at time of enrollment (PaO_2 / FiO_2) < 100 or > 250 in supine position
2. Intubated > 48h at time point of enrollment
3. Patients who demonstrate an improvement in past 24h prior to enrollment in oxygenation and ventilation / support parameters which indicate an expected resolution of lung dysfunction in the next 24h without additional intervention according to judgment of the investigator with one or more of the following parameters present:
4. Improvement in oxygenation index of > 30% relative to previous measure (last 24h in supine position)
5. Extubation if intubated before
6. Known history of chronic obstructive pulmonary disease (COPD) (GOLD category C or D)
7. Known history of chronic dialysis OR received renal replacement therapy in past 14 days
8. Received new other biologic treatment attempt for COVID-19 in the past 14 days
9. Received treatment with a viral replication inhibitor in past 3 days
10. Known hypersensitivity to IFX-1 or any other ingredient of the study medication
11. Known pregnancy
12. Received organ or bone marrow transplantation in past 3 months
13. Known mechanically resuscitation in past 14 days
14. Patient moribund or expected to die in next 12h according to the judgment of the investigator
15. Patients otherwise considered restricted from receiving full supportive care (including ICU support)

16. Existing diagnosis of progressed cancer or other life-limiting disease with life expectancy < 6 months
17. Known to have received anti-cancer therapy for oncological disease in past 4 weeks
18. Known severe congestive heart failure (New York Heart Association [NYHA] Class III-IV; see Appendix 8)

6.2. Phase III

6.2.1. Inclusion Criteria

Patients must meet all the following criteria at randomization to be enrolled into Phase III of the study:

1. At least 18 years of age or older
2. Patient on invasive mechanical ventilation (but not more than 48h post intubation at time point of randomization)
3. Patients with a PaO_2 / FiO_2 ratio of < 200 and > 60 at randomization (one representative measurement within 6h before randomization)
4. SARS-CoV-2 infection confirmation (tested positive in last 14 days before randomization with locally available test system)

6.2.2. Exclusion Criteria

Patients who fulfill any of the following criteria at randomization are not eligible to participate in Phase III of the study:

1. Intubated > 48h at time point of randomization
2. Expected stop of invasive ventilation or expected extubation in the next 24h without additional intervention according to judgment of the investigator
3. Known history of chronic dialysis OR received renal replacement therapy in past 14 days OR anticipated to receive renal replacement therapy within 24h after randomization
4. Known history of progressed COPD as evidenced by use of daily maintenance treatment with long-acting bronchodilators or inhaled/oral corticosteroids for > 2 months
5. Treatment of COVID-19 with investigational antibody treatment(s) which are not approved or not included in locally adopted treatment guidelines (e.g., WHO guidance, National Institutes of Health [NIH] COVID-19 treatment guidelines) for this indication in the past 7 days (Note: Antibody treatment[s] given within past 7 days for pre-existing diseases, other than COVID-19, are allowed.)
6. At time point of randomization, treatment of COVID-19 with investigational treatments which are not approved or not included in locally adopted treatment guidelines for this indication (e.g., WHO guidance, NIH COVID-19 treatment guidelines), including SARS-CoV-2 multiplication inhibitor(s) or immunomodulator(s). (Note: If a locally adopted treatment guideline recommends drugs such as remdesivir, dexamethasone, or

anticoagulation, this would be allowed. Adopted guidelines and updates must be documented at study initiation and throughout the conduct of the study.)

7. Known hypersensitivity to IFX-1 or any other ingredient of the study medication
8. Serum or urine pregnancy test positive before randomization (required for women of childbearing potential)
9. Received organ or bone marrow transplantation in past 3 months
10. Known cardio-pulmonary mechanical resuscitation in past 14 days
11. Received cytokine adsorption therapy in past 3 days
12. Patient moribund or expected to die in next 24h according to the judgment of the investigator
13. Known to have received anti-cancer therapy for hemato-oncological disease in past 4 weeks OR known to have active malignant disease at time point of randomization
14. Known severe congestive heart failure (NYHA Class III-IV; see Appendix 8)
15. Known history of chronic liver disease (Child-Pugh B or C; see Appendix 9)
16. Participating in or has participated in other investigational interventional studies (drug or device) within the last 7 days before randomization

6.3. Deferred Consent

In the Netherlands and Germany, we ask for deferred consent for patients in need of intensive care and we appeal to the emergency procedure for consent in medical research as stated in Article 6, Paragraph 4 of the WMO (Netherland), §41 (1) AMG (Germany), and other applicable country specific regulations, because of the following reasons:

It is very likely that the severity of the disease (severe pneumonia/acute respiratory distress syndrome) will result in a large proportion of patients unable to provide informed consent before the beginning of the trial either in oral or written form, mainly due to being on a ventilator or treated with drugs with sedative effects. COVID-19 related pneumonia resulting in the need for intensive care is a fast progressing disease. It requires immediate adequate treatment that cannot be postponed. So far, no treatment has been shown to address the underlying neutrophilic, inflammatory lung damage. Since IFX-1 blocks C5a, it has the potential to block neutrophil attraction to the lung. Moreover, it has been shown that COVID-19-related severe pneumonia is linked to extremely high C5a blood levels and related to a worse outcome of patients (Gao et al. 2020). In an ongoing study testing the biosimilar C5a antibody BDB-1, the first 2 patients treated showed a good recovery after being treated. Taken together, there is a possibility that treatment with IFX-1 will provide benefit specifically for patients with COVID-19-related severe pneumonia that require intensive care.

These severely ill patients are incompetent to give informed consent, and obtaining informed consent from a legal representative may be almost impossible due to the current COVID-19-

caused quarantine measures. Time to get informed consent from legal representatives will take at least half day, even by an experienced research team.

Patients will be randomized at the ICU where the inclusion and exclusion criteria will be checked directly before intensive care becomes necessary or during the 24 hours before invasive ventilation.

In the Netherlands, if the patient is incompetent to provide informed consent and a legal representative cannot be reached in time, the investigator examines the patient and confirms the patient's inability to provide consent as well as the urgency of participating in the trial with possible benefit to the patient. Informed consent from the patients, their relatives or their legal representative will be requested at the earliest appropriate time thereafter as applicable in the participating country. At minimum, the attempt of contacting the patient's relatives and the result of the contact will be documented in the patient's file.

In Germany, the investigator examines the patient and, if the patient is not able to consent, confirms together with a consulting physician, the patient's inability to provide consent as well as the urgency of participating in the trial with possible benefit to the patient. Informed consent from the patient will be requested at the earliest appropriate time thereafter. Due to the current lock down and quarantine regulations in Germany the patients' legal representative will not be contacted to obtain consent as it will be impossible to obtain written consent within the screening window.

In other participating countries where a deferred consent procedure is not legally acceptable, specific requirements will be laid out that will describe the country-specific legally acceptable procedure for retrieving consent from patients who are incompetent to provide consent or their relatives or their legal representatives, whatever will be applicable.

The hypothesis is that this group of intensive care patients can potentially benefit from participating in this study. While patients are exposed to the possible side effects of IFX-1, they will also receive SOC in Phase III.

6.4. Screening Failures

Screening failures are defined as patients who do not meet the criteria for participation in this study and thus, are not randomized/assigned to IMP. Screen failure data will not be recorded within the eCRF.

Rescreening does not apply to this study.

6.5. Meals and Dietary Restrictions

Not applicable.

7. STUDY DRUG(S) AND ADMINISTRATION

7.1. Investigational Medicinal Product

The IMP is defined as the investigational treatment IFX-1 and Placebo-to-match (Placebo) that is intended to be administered to a study patient according to the study protocol.

7.1.1. Packaging and Labelling of Investigational Medicinal Product

IFX-1 concentrate solution for infusion will be supplied in 20 mL glass vials at a concentration of 10 mg/mL (200 mg per vial) for reconstitution and IV administration. Apart from IFX-1, the solution will contain sodium chloride, sodium phosphate, and polysorbate 80.

Placebo concentrate solution for infusion will be supplied in 20 mL glass vials for reconstitution and IV administration. The solution will contain sodium chloride, sodium phosphate, and polysorbate 80.

IFX-1 and Placebo will be packaged in cartons and labeled in accordance with all legal requirements. Each carton will contain 4 vials of IFX-1 or 4 vials of Placebo. Each carton and each vial will be labeled with a multilingual booklet label or a single panel label as applicable.

7.1.2. Storage, Handling, and Accountability

Vials of IFX-1 and Placebo must be stored in a refrigerator at 2°C to 8°C (35.6°F to 46.4°F) in their original cartons to protect from light and must not be frozen or shaken. All supplies of IFX-1 and Placebo must be stored separately or segregated from other study supplies and site stock in a dedicated locked facility with access limited to authorized personnel. All storage facilities must be temperature controlled and monitored and compliant with applicable regulatory requirements.

An established and validated local temperature management system with temperature logs should be used to record the storage temperature. If this is not possible, the study site will be provided with a temperature record form by the Contract Research Organization (CRO) and the site personnel will maintain temperature records for the entire duration of the study. At a minimum, the daily (working day) minimum and maximum temperatures must be documented.

Any deviation from the specified temperature range must be documented and reported within 24 hours (or the next working day). Further instruction on the management and reporting of temperature deviations is provided in the Pharmacy Manual (or equivalent document).

The investigator or designee must confirm appropriate temperature conditions have been maintained during shipment for all IMP received and any discrepancies are reported and resolved before use of the IMP.

Only patients enrolled in the study may receive IMP and only authorized site staff may prepare and administer IMP. The IMP must be prepared in a controlled area in accordance with local regulations/ requirements for reconstitution of products for IV administration.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for the correct storage of IMP, IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMP are provided in the Pharmacy Manual (or equivalent document) provided by the CRO.

7.1.3. Drug Preparation and Administration Instructions

The IFX-1 and Placebo for infusion will be reconstituted (prepared) in a controlled area at the study site or at the study site's pharmacy, in accordance (compliance) with applicable local regulations/ requirements for reconstitution of products for IV administration.

The reconstituted IFX-1 or Placebo should be used within 4 hours after dilution when stored at room temperature. Otherwise, the reconstituted IFX-1 or Placebo has to be stored at 2°C to 8°C (35.6°F to 46.4°F) and used within 24 hours; if the reconstituted solution is stored in a refrigerator, it must be left to acclimatize to room temperature prior to administration. Details for the preparation of the reconstituted solution will be provided in the Pharmacy Manual (or equivalent document).

The number of unused, partially used, and empty vials will be documented accurately, and the vials will be kept at the site until further notice by the Sponsor.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Further guidance and information for the final disposition of unused IMP are provided in the Pharmacy Manual (or equivalent document).

7.1.4. Recall of IMP

Instructions (actions to be taken by site) in the case of IMP recall are provided in the Pharmacy Manual (or equivalent document).

7.2. Administration and Dosage

For Phase II, patients were randomized to either receive BSC + IFX-1 in treatment Arm A or BSC alone in treatment Arm B. The first dose of IFX-1 was administered at Cycle 1 Day 1.

For Phase III, patients are randomized to either receive SOC + IFX-1 in treatment Arm A or SOC + Placebo in treatment Arm B. The first dose of IFX-1 or Placebo is administered at Day 1.

Close observation of IFX-1 or Placebo infusion(s) is required for monitoring of potential infusion reactions. Appropriate treatment for potential infusion reactions must be available during this time.

7.2.1. Treatment Administered

7.2.1.1. Phase II

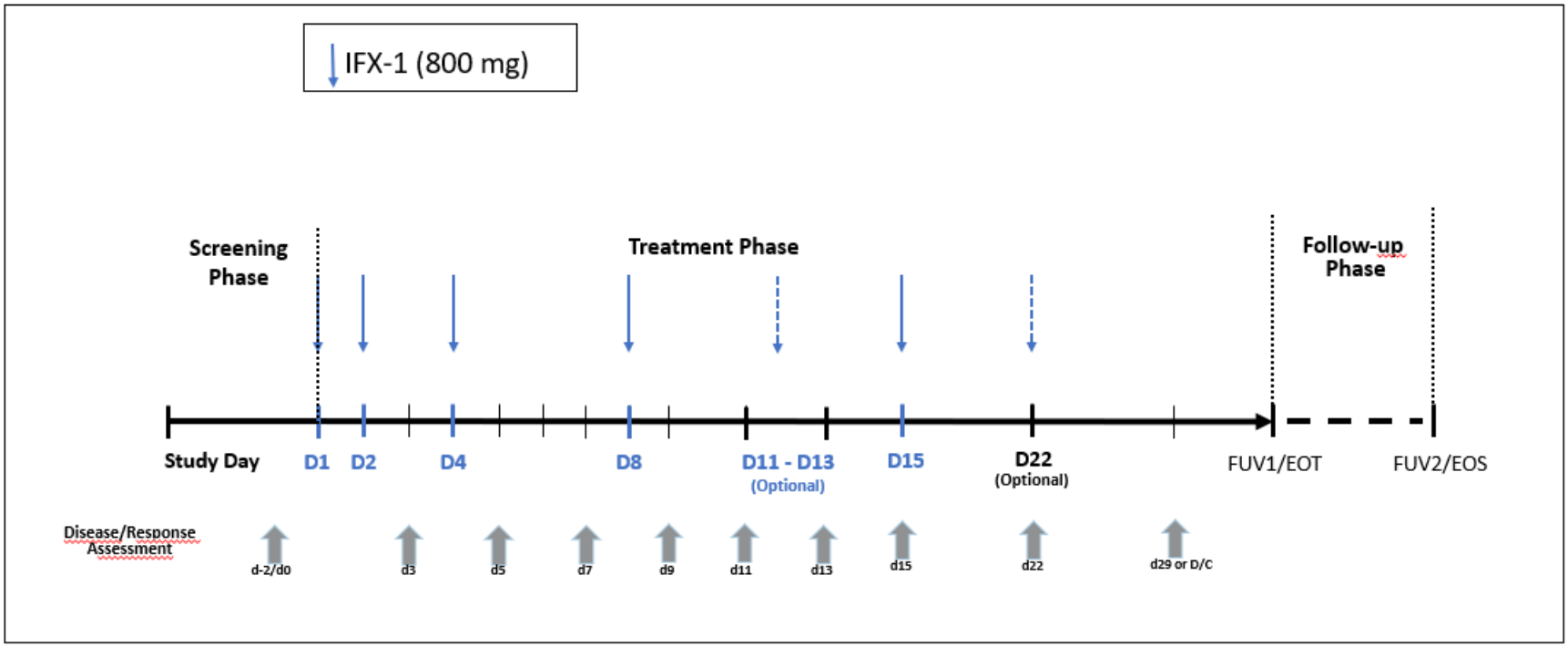
IFX-1 800 mg was administered for a maximum of 7 doses over a period of 29 days as a 30-minute IV infusion. However, given the variability of infusion pumps from site to site, a window between 5 minutes and +10 minutes was permitted (i.e., infusion time was 30 minutes (5 min/+10 min). IMP administrations for Phase II are detailed in Figure 1.

The first 5 treatments at days 1, 2, 4, 8, and 15 were administered to all patients randomized into Arm A. Treatment at day 22 was only administered in the event that a patient had not been extubated and discharged from ICU. In case a patient's clinical situation worsened after day 8, although an initial clinical benefit was observed, one additional administration of IFX-1 between day 11 and 13 could have been given at investigator discretion.

7.2.1.1. Phase III

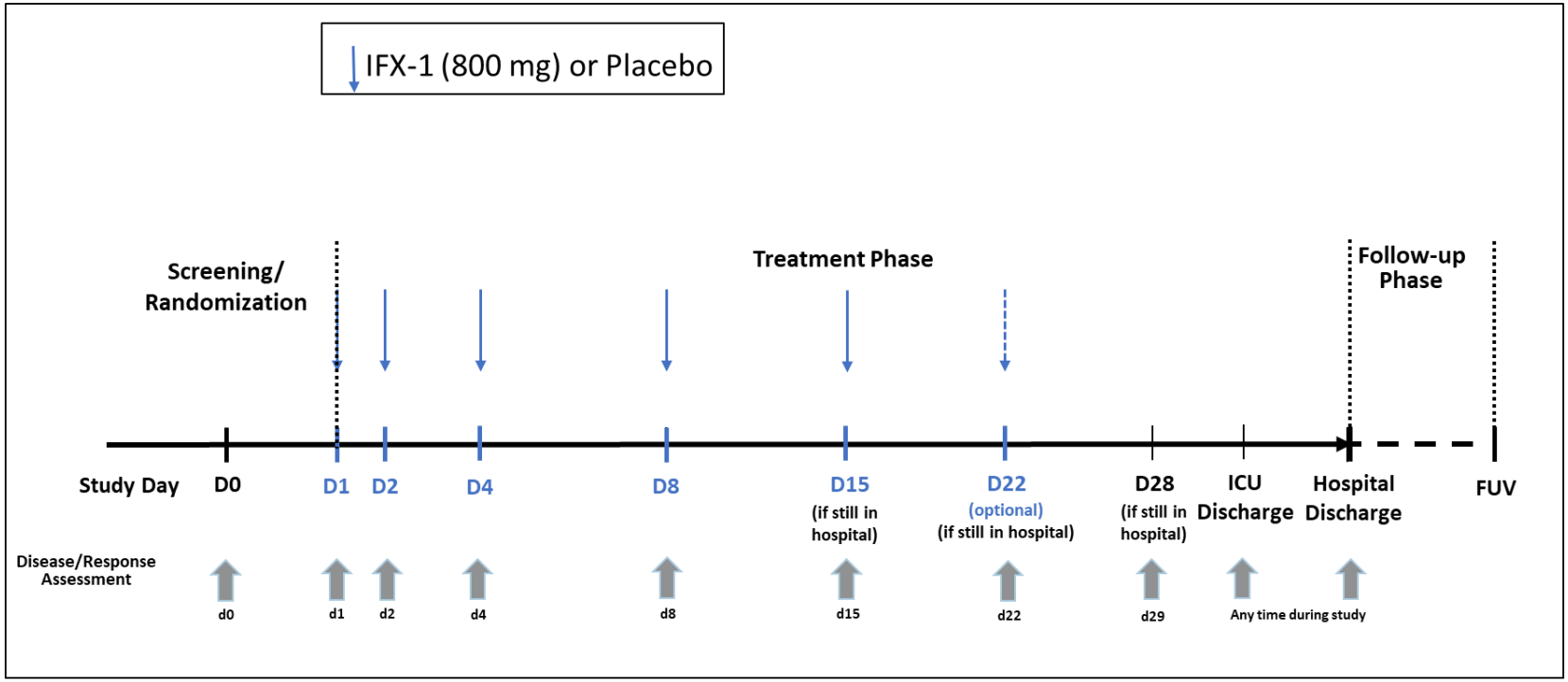
Patients will be treated with a maximum of 6 IV doses of IFX-1 800 mg (Arm A) or placebo (Arm B) administered as a 30-60 minute IV infusion. The first 4 treatments at days 1, 2, 4, and 8 shall be administered to all patients. Treatments at days 15 and 22 shall only be administered in the event that a patient is still in the hospital, even if discharged from ICU. IMP administrations for Phase III are detailed in Figure 2.

Figure 1 Patient Calendar: IMP Administrations – Phase II



D = day; D/C = discharge; EOS = end of study; EOT = end of treatment; FUV = follow-up visit; IMP = investigational medicinal product

Figure 2 Patient Calendar: IMP Administrations – Phase III



D = day; FUV = follow-up visit; IMP = investigational medicinal product

7.2.2. Treatment Modification

This protocol allows some alteration from the currently outlined dosing schedule, but a dose reduction of IMP is generally not allowed.

Adverse events leading to treatment modifications will be graded as mild, moderate, severe, or life-threatening based on the investigator's assessment, using the definitions provided in Section 9.2.2.

In case of toxicity, IMP dosing can be held by a maximum of 1 week. If therapy is continued during this time span, dosing will resume within the initial schedule and allowed administration window for a specific visit.

For treatment discontinuation criteria, see Section 7.2.4.

7.2.2.1. Infusion Reactions

IFX-1 may cause infusion reactions, including severe or life-threatening hypersensitivity or anaphylactic reactions. Signs and symptoms of infusion reactions usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion with or without adequate medication. Dose modification criteria for infusion reactions are listed in Appendix 5, Table 6.

7.2.3. Re-dosing Criteria

The following criteria must be fulfilled to allow for re-dosing of study drug:

- Absence of treatment discontinuation criteria (see Section 7.2.4).

7.2.4. Treatment Discontinuation Criteria

Discontinuation of study treatment does not represent withdrawal from the study. See Section 5.6.1.1 (for Phase II) or Section 5.6.2.1 (for Phase III) for the end of treatment definition and procedures.

In general, patients should be treated with IMP until unacceptable toxicity, completion of the planned treatment, extubation, or death.

Possible reasons for treatment discontinuation for individual patients are:

- Clinical deterioration
- Study participation consent withdrawal (see Sections 5.6.1.3 and 5.6.2.3)
- Safety:
  - moderate infusion reactions despite adequate premedication (see Appendix 5, Table 6)

- severe or life-threatening infusion reactions (see Appendix 5, Table 6)

7.3. Premedication and Postmedication

Routine premedication is not required prior to the first dose of IMP.

Patients with mild or moderate infusion reaction following IMP administration may continue to receive IMP with close monitoring; premedication with antipyretic and antihistamine may be considered.

Patients should be observed for 60 minutes, or longer per clinical judgment, after IMP administrations.

Treatment guidelines in case of occurrence of infusion reactions are detailed in Appendix 5, Table 6.

7.4. Prior and Concomitant Medication/Treatments

In Phase III of the study, in addition to the IMP, all patients will receive SOC for treatment of COVID-19, which includes VTE prophylaxis with anticoagulants at a minimum. Other international or country-specific recommended treatments for COVID-19 per the locally adopted treatment recommendations (including but not limited to corticosteroids, remdesivir, and other local SOC) are allowed as concomitant medications.

Reporting of prior and concomitant medications will follow special considerations for the ICU setting, as described in Appendix 10.

Reportable medications or vaccinations that the patient is receiving within 7 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded along with:

- Reason for use
- Dates of administration including start and end dates

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.4.1. Prohibited Concomitant Medication/Treatment

Medications or vaccinations specifically prohibited in the exclusion criteria (see Sections 6.1.2 and 6.2.2) are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy may be required. The investigator should discuss any questions regarding this with the medical monitor. The final decision on any supportive therapy or vaccination rests with the

investigator and/or the patient's primary physician. However, the decision to continue the patient on study treatment requires the mutual agreement of the investigator and the sponsor.

The following concomitant therapies or vaccinations are prohibited during the course of the study:

- Antineoplastic systemic therapy
- Investigational antibody treatments and other investigational agents (excluding IFX-1 but including SARS-CoV-2 multiplication inhibitor[s] or immunomodulator[s]) which are not approved or not included in locally adopted treatment recommendations for treatment of COVID-19 (e.g., WHO guidance, NIH COVID-19 treatment guidelines)
- Cytokine adsorption therapy

Patients who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

7.5. Rescue Medications and Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator.

7.6. Treatment of Overdose

No specific information is available on the treatment of overdose of IFX-1. For this study, an overdose of IFX-1 will be defined as any single dose of > 1200 mg. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately
2. Closely monitor the patient for any AE/SAE and laboratory abnormalities
3. Obtain a plasma sample for PK analysis as close as possible to the administration of overdose if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the patient.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Phase II

Study procedures and their timing for Phase II are summarized in the Schedule of Assessments (SoA; Table 1).

Details on the assessments and procedures are given in the following subsections.

Safety concerns should have been discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue any IMP.

Adherence to the study design requirements, including those specified in the SoA (Table 1), was essential and required for study conduct.

All screening evaluations must have been completed and reviewed to confirm that potential patients met all eligibility criteria (Section 6.1). The investigator was to maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1.1. Baseline Assessments

The following procedures were to be performed to assess baseline characteristics during screening evaluations and before IMP administration:

- Documentation of demographic details (age, gender, race, and ethnicity), medical and disease history (see Sections 8.1.1.1 and 8.1.1.2)
- Disease assessments (see Section 8.1.2)
- Documentation of concomitant disease and concomitant medications (see Sections 8.1.1.3 and 8.1.1.4)
- Baseline safety assessment (height, weight, physical exam, vital signs, AEs, and safety laboratory; see Section 8.1.3)

8.1.1.1. Medical History (Except COVID-19 history)

The documentation of the patient's medical history were to include any details on the patient's medical history before enrollment into the study. The information must have been documented as such in the source documentation and eCRF.

8.1.1.2. COVID-19 History

Any details on the patient's COVID-19 disease history including any COVID-19 therapy (onset of symptoms, medications, oxygen support, intubation, SARS-CoV-2 testing) by verbatim name with start and end dates, dosages, modality) that the patient received were to be documented in the source documentation and in the eCRF.

8.1.1.3. Concomitant Disease

All diseases that the patient was experiencing at enrollment into the study or after enrollment until EOT were to be regarded as concomitant diseases. All concomitant diseases must have been documented in the source documentation and in the eCRF.

8.1.1.4. Prior and Concomitant Medications

All drugs being taken by a patient at enrollment into the study or after enrollment until EOT were to be regarded as concomitant medication.

All prior medications taken by the patient within 2 weeks before enrollment into the study and all concomitant medications must have been documented in the source documentation and in the eCRF. Details on prior and concomitant medications must have included the reason for use, administration start and stop dates, and dosing information, including dose, route, and frequency of administration.

8.1.2. Efficacy Assessments

8.1.2.1. Imaging Requirements

CT scan, MRI, or X-ray for COVID-19 assessment were to be performed locally at each scheduled disease assessment time point, and at any time when disease progression was suspected.

The choice of whether the imaging was by CT scan, MRI, or X-ray was an investigator decision. Once the imaging choice had been made, subsequent assessments should have been made using the same modality whenever possible.

8.1.2.2. Evaluation of Lung Function

- Oxygenation index (PaO_2 / FiO_2)
- Respiratory rate
- Oxygen supplementation: room air, flow O_2 (L/min) if extubated
- Ventilation status (invasive/non-invasive/intermittent non-invasive)
- Mode of ventilation (e.g., CPAP/BIPAP)
- Other oxygenation support
    - Type of oxygen mask or nasal canula, or other mechanical ventilation mode and parameters, as applicable, should have been documented
- Intubation and extubation dates, as well as date of tracheostomy should have been documented

8.1.2.3. Evaluation of Response

- SARS-CoV-2 mRNA testing was to be performed in context of enrolment procedures and at one to four additional time points at discretion of the investigator

8.1.2.3.1. Evaluation of Early Response

Early Response as defined as meeting ALL of the following criteria at day 7 after enrollment:

- Patient alive and extubated OR oxygenation index ≥ 300 OR improvement of ≥ 30% from baseline,
- Temperature < 38°C in absence of fever decreasing medication of at least 4h
- White blood cell count within normal limit of local lab quantifications

8.1.2.3.2. Evaluation of Late Response

Late Response as defined by either being **discharged alive** from hospital until day 28 **OR** meeting **ALL** of the following criteria at day 28 of the trial:

- Patient alive and extubated
- Patient discharged from ICU
- Patient free of shortness of breath (respiratory rate < 20) in absence of oxygen supply
- Patient free of fever (< 37.6°C)

8.1.3. Safety Assessments

Safety was to be assessed based on the following variables:

- AEs (see Section 8.1.3.1)
- Laboratory safety parameters (see Section 8.1.3.2)
- Vital signs (see Section 8.1.3.3)
- Electrocardiograms (see Section 8.1.3.4)
- Physical examination (see Section 8.1.3.5)

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.1.3.1. Adverse Events Assessments

Adverse events were to be assessed throughout the study from the time of enrollment to the EOT visit as specified in the SoA (Table 1). For details on AE collection and reporting, see Section 9.1. The investigator should have taken appropriate measures to follow all AEs until clinical recovery was complete and laboratory results had returned to normal, or until progression had been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations would continue beyond the last planned visit per protocol, and that

additional investigations may have been requested by the sponsor. When study treatment was prematurely discontinued, the patient's observation was to be continued until the EOT visit for that patient as defined by the protocol.

8.1.3.2. Clinical Safety Laboratory Assessments

In general, blood samples for safety laboratory analysis should have been obtained once a day during a routine sampling (preferable in the morning) before administration of IMP. Additional tests may have been performed at any time during the study as determined necessary by the investigator or required by local regulations.

See Appendix 1, Table 3 for the list of clinical laboratory tests performed and the SoA (Table 1) for timing and frequency.

The investigator must have reviewed the laboratory report, documented this review, and recorded any clinically relevant changes (clinically relevant abnormal findings) occurring during the study in the AE section of the eCRF. The laboratory reports must have been filed with the source documents. Clinically relevant abnormal laboratory findings were those which were not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically relevantly abnormal and with onset before EOT visit should have been reported in the AE section of the eCRF and repeated until the values returned to normal or baseline, were no longer considered clinically relevant by the investigator or medical monitor, or until the EOS visit (also see Section 8.1.4 and Appendix 3).

If such values did not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should have been identified, and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 1, Table 3, must have been conducted in accordance with the SoA (Table 1).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory required a change in patient management or were considered clinically relevant by the investigator (e.g., SAE or AE or dose modification), then the results must have been recorded in the eCRF.

Blood samples for serum pregnancy testing were to be collected on the same day as safety laboratory testing. For details on pregnancy testing, refer to Appendix 4.

8.1.3.3. Vital Signs

Core body temperature, heart rate, respiratory rate, and blood pressure (diastolic and systolic) were to be assessed at each visit at pre-dose on the days of IMP administration and at further time points whenever medically indicated.

Blood pressure and pulse measurements were to be assessed with a completely automated device. Manual techniques were to be used only if an automated device was not available.

Vital signs were to be measured in a supine position (after a rest of at least 1h in case of position switch from prone position), preferably in the morning. Three readings of blood pressure and pulse were to be taken. The first reading should have been rejected. The second and third readings should have been averaged to give the measurement recorded in the eCRF.

8.1.3.4. Electrocardiograms

12-lead electrocardiogram (ECG) was to be obtained as outlined in the SoA (Table 1) using an ECG machine that automatically calculated the heart rate and measured PR, QRS, QT, and QTc intervals.

8.1.3.5. Physical Examination

A physical examination was to be conducted at screening and each study visit.

The physical examination included, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (at screening) and weight was also to be measured and recorded as specified in the SoA (Table 1).

Investigators should have paid special attention to clinical signs related to previous serious illnesses.

8.1.3.6. Survival Status

The patient survival status were to be assessed during the study and follow-up and documented in the eCRF. In case the patient died and the date of death was unknown, the date of the last personal contact should have been documented at a minimum.

8.1.4. Pharmacokinetics/Pharmacodynamics

If possible, blood samples were to be collected pre-dose for measurement of plasma concentrations and C3a and C5a of IFX-1 as specified in the SoA (Table 1). IFX-1 concentrations were to be measured for all patients in citrate plasma and analyzed by a specialized laboratory using Enzyme-Linked ImmunoSorbent Assay.

Detailed instructions regarding the collection, processing, etc., of samples were to follow local regulations and requirements.

8.1.5. Biobanking of Samples from Patients Treated at Amsterdam Medical Center

COVID-19 is a new viral disease with distinct clinical and pathophysiological features, which differentiate COVID-19 from other viral diseases such as Influenza. A COVID-19 dedicated Biobank was established at the Amsterdam Medical Center (AMC) in order to investigate further

COVID-19 pathophysiological characteristics. Therefore, it was planned to store all remaining AMC study patient derived biomaterials, including but not limited to blood, bronchial lavage fluid, and tissue in the AMC COVID-19 Biobank. Patients were to be asked for a separate informed consent.

8.2. Phase III

Study procedures and their timing for Phase III are summarized in the SoA (Table 2).

Details on the assessments and procedures are given in the following subsections.

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue any IMP.

Adherence to the study design requirements, including those specified in the SoA (Table 2), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria (Section 6.2). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.2.1. Baseline Assessments

The following procedures will be performed to assess baseline characteristics during randomization evaluations and before IMP administration:

- Check inclusion and exclusion criteria
- Documentation of demographic details (age, gender, race, and ethnicity), medical and COVID-19 history (see Sections 8.2.1.1 and 8.2.1.2)
- Ordinal scale assessment (see Section 8.2.2.2) and oxygenation index (PaO_2 / FiO_2; one representative measurement within 6h before randomization)
- Documentation of concomitant disease and prior medications (see Sections 8.2.1.3 and 8.2.1.4)
- Baseline safety assessment (height, weight, physical exam, AEs, ECGs, urine analysis, pregnancy test, and clinical safety laboratory [including creatinine assessment]); see Section 8.2.3)

8.2.1.1. Medical History (Except COVID-19 history)

The documentation of the patient's medical history includes any details on the patient's medical history before randomization into the study. The information must be documented as such in the source documentation and eCRF.

8.2.1.2. COVID-19 History

Any details on the patient's COVID-19 disease history including any COVID-19 therapy (onset of symptoms, medications, oxygen support, intubation and tracheostomy dates, SARS-CoV-2 polymerase chain reaction (PCR) test date and result by verbatim name with start and end dates) that the patient received will be documented in the source documentation and in the eCRF.

8.2.1.3. Concomitant Disease

All diseases that the patient is experiencing at screening/randomization until end of treatment are regarded as concomitant diseases. All concomitant diseases must be documented in the source documentation and in the eCRF.

8.2.1.4. Prior and Concomitant Medications and Procedures

All procedures performed or medications administered within 7 days before randomization should be recorded as prior procedures and prior medication with generic name, start date, stop date, and indication for treatment.

Reporting of prior and concomitant medications will follow special considerations for conditions in the ICU. A complete record of all prior and concomitant medications (but excluding nutritional and volume therapy, electrolyte support, vitamins, non-steroidal anti-inflammatory drugs (NSAIDs), and supportive therapies such as artificial tears, ointments, stool softeners/laxatives, etc.) will be maintained in the eCRF for each participant, beginning at baseline and continuing until day 28 or hospital discharge (whatever occurs earlier).

In addition, a complete record of all steroid and antibiotic therapy, as well as any therapy (medications, specific treatments, etc.) associated with or used in the assessment or treatment of an AE will be documented for the duration of the study.

The following information must be recorded in the eCRF for each reportable concomitant medication: generic name, route of administration, start date, stop date, and indication (Appendix 10).

8.2.2. Endpoint Assessments

8.2.2.1. Evaluation of Organ Support

- Renal replacement therapy, extracorporeal membrane oxygenation (ECMO), mechanical ventilation
- Extubation and re-intubation dates should be documented

8.2.2.2. Ordinal Scale Evaluation

Ordinal scale score will be documented at the visits specified in the SoA (Table 2), including the date (one value per assessment day, that best represents the patient's condition at that day).

8.2.2.3. Survival Status

The patient's survival status will be assessed during the study and at the day 60 FUV and will be documented in the eCRF. In case the patient has died and the date of death is unknown, the date of the last personal contact should be documented at a minimum.

8.2.2.1. Quality of Life Assessment

If possible, patients will be assessed for quality of life using the EQ-5D at the day 60 FUV.

8.2.2.2. Clinical Status

Patient's clinical status will be assessed by the Glasgow Outcome Scale at the day 60 FUV.

8.2.3. Safety Assessments

Safety will be assessed based on the following variables:

- AEs (see Section 8.2.3.1)
- Laboratory safety parameters, including creatinine (see Section 8.2.3.2)
- Vital signs (see Section 8.2.3.3)
- Electrocardiograms (see Section 8.2.3.4)
- Physical examination (see Section 8.2.3.5)

Planned time points for all safety assessments are provided in the SoA (Table 2).

8.2.3.1. Adverse Events Assessments

Adverse events will be assessed throughout the study as specified in the SoA (Table 2). Adverse event reporting will follow special considerations for the ICU setting as described in Appendix 3.

8.2.3.2. Clinical Safety Laboratory Assessments

In general, blood samples for safety laboratory analysis and creatinine assessment should be obtained at indicated visit days during routine sampling (one representative value, if taken more than once a day). Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

See Appendix 1, Table 4 for the list of clinical laboratory tests to be performed and the SoA (Table 2) for timing and frequency.

In clinical studies conducted in the ICU, deviations in laboratory values are to be expected frequently. Clinical judgement should be applied in determining which deviations should be reported as an AE in the sense of an "untoward medical occurrence" and which deviations should be considered usual and expected findings in this setting.

It must be noted that clinically relevant laboratory deterioration as assessed by the investigator with onset before end of treatment must be documented in the respective eCRF section. However, it is preferred to document the condition or disease underlying the aberrant laboratory value (e.g., renal failure rather than hyperkalemia) rather than the laboratory value only.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant, and thus constitutes an AE (see also Section 9 and Appendix 3).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory fulfill the aforementioned criteria for clinical significance, then the results must be recorded in the eCRF.

All protocol-required laboratory assessments, as defined in Appendix 1, Table 4, must be conducted in accordance with the SoA (Table 2).

Urine analysis (dipstick) and serum or urine samples for pregnancy testing will be collected only at screening/randomization. For details on pregnancy testing, refer to Appendix 4.

8.2.3.3. Vital Signs

Vital signs (core body temperature, heart rate, respiratory rate, blood pressure [diastolic and systolic]) will be assessed at indicated visits at pre-dose within 1h before administration of IMP (one representative measurement closest to IMP administration) and at further time points whenever medically indicated. Blood pressure and heart rate measurements will be assessed with an intra-arterial catheter, or a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3.4. Electrocardiograms

12-lead ECG will be obtained as outlined in the SoA (Table 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.2.3.5. Physical Examination

A physical examination will be conducted at the time of randomization and on the days of IMP administration, as specified in the SoA (Table 2).

The physical examination includes, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.

8.2.4. Pharmacokinetics/Pharmacodynamics

PK/PD testing will be done at selected sites in the US, Europe, and Russia. Blood samples will be collected for measurement of plasma IFX-1 concentrations, C5a, and ADAs of IFX-1 within 1h before administration of IMP, as specified in the SoA (Table 2).

Detailed instructions regarding the collection, processing, etc., of samples will follow local regulations and requirements.

9. ADVERSE EVENT COLLECTION AND REPORTING

All AEs, serious and non-serious (see Appendix 3 I for definitions), must be collected, documented, and reported from randomization onwards until the end of treatment (see Section 9.1.1). They will be further followed up until the end of study (see Section 9.1.1.1), however death and related SAEs with onset during the follow-up period and after the end of study will be collected and reported (see Section 9.1.2).

All AEs will be reported to the sponsor by the investigator in the appropriate sections of the eCRF. It will be specified whether the event is serious or not according to the definition of SAE (see Appendix 3 I). In case of an SAE, the SAE report will be processed by the safety vendor (see Section 9.2.1). The safety vendor for this study is IQVIA Pharmacovigilance. Reporting of AEs will be done according to the specific definitions and instructions for completing the respective sections of the eCRF.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE and remain responsible for following up AEs, considered related to the IMPs or study procedures (see Section 9.2.2 and Appendix 3 II for details on causality of AEs), or that caused the patient to discontinue study treatment (see 7.2.4 for treatment discontinuation criteria) or the study.

Care will be taken not to introduce bias when detecting AEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

Due to the severity of disease of the patient population entering this study, numerous problems, signs, and symptoms deviating from normal will be seen during the course of the study. These will not necessarily constitute a reportable AE unless they require significant intervention, lead to discontinuation of blinded study drug, or are considered to be of concern in the investigator's clinical judgement. Similarly, it is preferred to receive documentation of the underlying condition rather than the resulting sign (e.g., 'agitation' rather than 'self-extubation').

In clinical studies conducted in the ICU, deviations, e.g., in laboratory values or temporary changes in arterial blood pressure, are to be expected frequently. Clinical judgement should be applied in determining which deviations should be reported as an AE in the sense of an "untoward medical occurrence" and which deviations should be considered usual and expected

findings in this setting. It is preferred to document the condition or disease underlying the aberrant laboratory value (e.g., renal failure rather than hyperkalemia) rather than the laboratory value only.

The records will describe (Appendix 3 II) the nature (diagnosis or single syndrome if possible, alternatively signs and symptoms), severity (mild, moderate, severe, life-threatening, fatal), start date and time, stop date and time, actions taken with respect to the IMP, corrective treatment/therapy given, additional investigations performed, outcome, and causality (relationship to study treatment according to the investigator's assessment; see also Section 9.2.2).

The terms 'disease progression', 'progressive disease', or similar, do not constitute an acceptable description of the nature of an AE. For example, if a patient experiences disease progression with hemoptysis leading to hospitalization, the investigator should file an AE and an SAE for the hemoptysis; data related to disease progression should be captured in the disease assessment and response evaluation section of the eCRF.

Any AE not listed as an expected event in the IB or in this protocol will be considered unexpected.

9.1. Time Period and Frequency of Collection and Reporting

The following timeframes for reporting apply from signature of the informed consent on:

- All AEs, including AESIs and SAEs until 30 days following the last IFX-1 administration must be reported
- All pregnancies until 9 months after the last dose of treatment must be reported, as described in Section 9.5.2

Any time outside of the time period specified above, in addition, any study drug related SAE brought to the attention of an investigator must be reported immediately to the sponsor.

9.1.1. During Treatment

All AEs, including SAEs and AESIs, must be collected from the time of patient signing the consent form until 30 days following the last IFX-1 administration must be reported.

- All AEs must be followed until the outcome of the event is 'recovering' (for stabilization of chronic conditions), or recovered (/with sequelae), and until all queries related to these AEs have been resolved.
- Ongoing AEs should be reviewed at each scheduled and unscheduled visit until the hospital discharge visit. If resolved, the details should be recorded in the eCRF. If any AE changes for the worse, in frequency of attacks/symptoms or in severity, a new record of the event must be started (i.e. distinct reports are required for differing frequencies and/or severity of the same event to enable comprehensive safety reports and later analysis).

- If the patient dies from an event, ongoing further AEs can be closed with an outcome 'unknown', if outcome was not assessed at day of death.

9.1.1.1. During Follow-up

All ongoing AEs with onset in the treatment period will have to be followed up after the hospital discharge visit until the outcome of the event is 'recovering' (for chronic conditions), or recovered (/with sequelae), or until end of study and until all queries related to these AEs have been resolved.

All SAEs, including fatal events related to IMP with onset during the follow-up period (from the hospital discharge visit until end of study) will have to be collected and followed until resolved.

9.1.2. After End of Study

After the end of study, new SAEs related to IMP must be reported to the sponsor via the regular SAE reporting system.

9.2. Serious Adverse Event Reporting and Timelines

9.2.1. Initial Reporting of Serious Adverse Events

SAEs that should be reported within 24 hours on the SAE form are:

- Events with fatal outcome
- New life-threatening events, defined as:
  - Cardiac event requiring CPR or medical resuscitation (adrenaline use etc.) – can be caused by severe arrhythmia or other
  - Life-threatening spontaneous bleeding requiring blood transfusion and / or surgical intervention
  - Thrombo-embolic event with life-threatening hemodynamic or pulmonary instability
  - New life-threatening organ failure / dysfunction
    - Liver: AST, ALT > 20 x upper limit of normal (ULN) OR Bilirubin > 10 x ULN
    - Kidney: Creatinine > 6 x ULN – or newly developed anuria ≤ 100 mL urine production over 24h
    - Cardiovascular:
      - Norepinephrine > 1 µg/Kg/min or equivalent
      - Troponin I: levels consistent with myocardial infarction as defined by manufacturer
    - Coagulation: Thrombocyte count < 20.000 / µL or PTT > 2.5 x ULN

- Life-threatening infections other than COVID-19 which require immediate antibiotic treatment and/or additional medical / surgical intervention
- Life-threatening infusion reactions which require immediate intensification of existing intensive care treatment, including but not limited to additional vasopressor of fluid support, or high dose corticosteroids and antihistamines

All remaining SAEs should be reported at investigator's earliest convenience. SAEs should be approved by the investigator (see Appendix 3 II). In addition, SAEs need to be reported in the (non-serious) AE section of the eCRF. The investigator will be requested to supply as much detailed information regarding the event as is available at the time of the initial contact.

For transmission of the back-up paper-based SAE form, please use the following FAX line or e-mail account:

Fax: +353 1 809 9501

QLS_IFX1@iqvia.com

In addition, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical study are properly mentioned on any copy of a source document provided to the sponsor. For laboratory results, the investigator must include the laboratory normal ranges.

9.2.1.1. Follow-up Reporting of Serious Adverse Events

Follow-up information on SAEs must be reported by the investigator within the same time frames as the initial reporting.

A follow-up report to an SAE should be prepared if any relevant change in the condition of the patient occurs after the initial report, or any new relevant information becomes available.

Further information on follow-up procedures is given in Appendix 3 II.

9.2.2. Determination of Relatedness

The investigator will use medical consideration to determine the relatedness of an AE with the study drug based on the following definitions (see also Appendix 3 II):

Unrelated

This category applies to AEs that are due to extraneous causes (disease, concomitant medication, environment, etc.) and are not related to the administration of study drug.

Unlikely Related

This category applies to AEs that are unlikely related to the administration of the study drug. The relationship of an AE to the study drug can be considered unlikely related if (must have first two criteria listed below):

- The AE does not follow a reasonable temporal sequence from administration of the drug
- The AE could readily have been a result of the patient's clinical state or other underlying medical condition, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE does not follow a known response pattern to the suspected drug
- The AE does not reappear or worsen when the study drug is re-administered

Possibly Related

This category applies to AEs that are unlikely to be related to the administration of the study drug, but the possibility cannot be ruled-out with certainty. The relationship of an AE to the study drug can be considered possibly related if (must have first two criteria listed below):

- The AE follows a reasonable temporal sequence from administration of the study drug
- The AE could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE follows a known response pattern to the suspected study drug

Probably Related

This category applies to AEs that are considered with a high degree of certainty to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered probably related if (must have first three criteria listed below):

- The AE follows a reasonable temporal sequence from administration of the study drug
- The AE could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE disappears or decreases upon cessation of study drug or reduction in dose
- The AE follows a known response pattern to the suspected study drug

Definitely Related

This category applies to AEs that are determined with certainty to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered definitely related if (must have first three criteria listed below):

- The AE follows a reasonable temporal sequence from administration of the study drug or study drug levels have been established in body fluids or tissues

- The AE could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE disappears or decreases upon cessation of study drug or reduction in dose and, if applicable, appears upon re-challenge
- The AE follows a known response pattern to the suspected study drug
- There are exceptions when an AE does not disappear upon discontinuation of the study drug, yet study drug relatedness clearly exists; e.g., 1) tardive dyskinesia, 2) fixed drug eruptions

9.3. Death Reporting

The site should follow all patients for survival and collect information around the death on the appropriate eCRF form until the end of the study.

Primary cause of death should be reported in AE section and SAE form, as well as appropriate eCRF section(s). If symptoms of disease progression occurred and constitute the primary cause of death, these symptoms could be reported as fatal (S)AE (see Section 9.2.2).

9.4. Abnormal Laboratory Values/Vital Signs/ECG/Physical Examination

Abnormalities of laboratory results / vital signs / ECG / physical examination should be reported as AEs, particularly if at least one of the following is met:

- Any criterion for an SAE is fulfilled
- The abnormality causes the patient to discontinue from the study treatment
- The abnormality causes the patient to interrupt the study treatment or a modification of dosing
- The abnormality requires intervention as corrective treatment or consultation
- The investigator judges that the abnormality is clinically relevant and should be reported as an (S)AE in the eCRF

All laboratory tests for which abnormal results are collected after the initiation of study treatment should be repeated until the values return to normal or to a stable status. If abnormal results are outside of the normal laboratory range and also assessed as clinically relevant by the investigator, they must be reported as an AE. The frequency with which such checks should be made will be made by investigator's discretion depending on the degree of abnormality. The reporting of laboratory/vital signs/ECG/physical examination abnormalities as both AEs and a specific finding of laboratory values/vital signs/ECG should be avoided.

Abnormal laboratory value testing will follow special considerations for conditions in the ICU. It must be noted that clinically relevant laboratory deterioration as assessed by the investigator must be documented in the respective eCRF section. However, it is preferred to document the

condition or disease underlying the aberrant laboratory value (e.g., renal failure rather than hyperkalemia) rather than the laboratory value only.

9.5. Events to be Handled as SAEs

9.5.1. Overdose Reporting

An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically relevant.

All symptoms associated with the overdose should be handled as SAEs.

Refer to Section 7.6 for details on the treatment of overdose.

9.5.2. Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant during treatment or within 9 months after the last dose of treatment, the investigator should report the pregnancy to QLS_IFX1@iqvia.com via e-mail within 24 hours of being notified. The safety vendor will then forward the pregnancy reporting form to the investigator for completion. In case that e-mail contact is not possible, the site can provide an initial pregnancy report in the SAE section of the SAE form and transmit this via the SAE FAX line: +353 1 809 9501.

A patient becoming pregnant while on IMP will immediately be discontinued from treatment and the EOT visit will be performed.

The patient or partner should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the sponsor. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting as SAE.

9.5.3. Drug-induced Liver Injury

Potential drug induced liver injury is considered an important medical event. Although it is not always serious by regulatory definition, such event must be handled as SAE.

Wherever possible, timely confirmation within 48 to 72 hours of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug induced liver injury event. All occurrences of potential drug induced liver injuries, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

- ALT or AST elevation > 3 × ULN

AND

- Total bilirubin >2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

- No cholestatic or other immediately apparent possible causes of AST or ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

9.5.4. Suspected Transmission of an Infectious Agent (pathogenic or non-pathogenic) via Study Drug

For the purposes of reporting, any suspected transmission of an infectious agent via the investigational drug should be considered as an SAE.

A transmission of an infectious agent may be suspected from clinical signs or symptoms, or laboratory findings indicating an infection in a patient exposed to a medicinal product.

In the context of evaluating a suspected transmission of an infectious agent via a medicinal product, care should be taken to discriminate, whenever possible, between the cause (e.g., injection/administration) and the source (e.g., contamination) of the infection and the clinical conditions of the patient at the time of the infection (immuno-suppressed /vaccine).

9.6. Adverse Events of Special Interest

AESIs are events that are considered to have a special meaning or importance for a particular drug or class of drugs. They may be non-serious or serious. Therefore, they should be closely monitored. The site must report all AESIs that occur during the study period, whether considered to be related to IP or not, according to Appendix 3. Moreover, AESIs should be documented in the general AE section of the eCRF as well as in the patient file.

This is the first study investigating IFX-1 in COVID-related pneumonia. Clinical experience with IFX-1 has been generated in more than 300 patients with inflammatory diseases, including sepsis and HS.

For this study, the following AEs are defined as AESIs:

- Infusion reactions, including hypersensitivity or anaphylaxis during or after IFX-1 infusion:

  All patients should be observed closely during the IFX-1 administration and for ≥ 60 minutes thereafter. The intravenous line should remain open during the observation to allow for administration of intravenous drugs, if necessary. Medication for infusion reactions should be available for immediate use. Medical staff has to be trained in resuscitation and immediate intensive care has to be easily accessible in case of severe

life-threatening events. Mild to moderate reactions may be treated by slowing or interruption of the infusion, or with supportive treatment (Appendix 5).

For any potential infusion event, the investigator should closely monitor for a potentially developing or existing anaphylactic reaction. In case an anaphylactic reaction is anticipated, appropriate immediate actions should be taken according to the severity or stage of the detected anaphylactic reaction.

- Meningitis and meningococcal sepsis:

  In case of signs of meningitis at any time during the study, the IMP should be discontinued if meningitis is confirmed. The patient must be closely monitored and the guidelines for treatment of meningitis should be followed (Tunkel et al. 2004, van de Beek et al. 2016). This includes lumbar puncture, blood culture testing, immediate start of treatment with dexamethasone and intravenous antibiotics (combination therapy with ampicillin and third generation cephalosporin), and a search for the focus of the infection (e.g., CT or MRI).

- Infections other than COVID-19 (SARS-CoV-2) infections

  In patients with bacterial infection, depending on the severity of the infections, it is important that concomitant antibiotic therapy is administered during treatment with IFX-1 to ensure appropriate control of the source of the infection. The investigator should pay close attention to the choice of an appropriate broad-spectrum antibiotic treatment according to applicable guidelines.

  Note: A severe infection can be suspected whenever an IV antibiotic, antifungal, or antiviral intervention would be indicated under non-ICU conditions or an invasive intervention would have been indicated.

9.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Disease progression does not constitute an AE itself; however, the symptoms/diagnosis leading to disease progression must be reported as AE or SAE accordingly.

9.8. Reporting to Competent Authorities and Ethics Committees

The IB(s) will be the reference document for reference safety information.

The safety vendor is responsible for submission of suspected unexpected serious adverse reactions (see Appendix 3 I for a definition) to health authorities and Institutional Review Boards (IRB)/Independent Ethic Committees (IEC) in accordance with local regulations.

The investigator is responsible for informing the IRB/IEC in a timely manner and in accordance with local procedures.

10. STATISTICAL CONSIDERATIONS

10.1. Phase II

10.1.1. Sample Size Determination

No formal sample size calculation was performed for this trial. The sample size was based on pragmatic considerations in this new and urgent setting with very limited knowledge about the disease.

For the Phase II part of the trial 30 patients were randomized in a 1:1 ratio to treatment Arm A (SBC + IFX-1) and Treatment Arm B (BSC).

10.1.2. Analysis Sets

All analyses were to be performed based on all randomized patients.

10.1.3. Statistical Analyses

The statistical analysis plan (SAP) was developed and finalized as soon as possible after clinical trial application approval. The SAP includes the exact definition of endpoints and variables to be analyzed, extensive details on the statistical analysis methods to be used together with the structure of tables and figures to be included as end-of-text tables and figures as well as appended listings for the clinical study report. It also describes procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints for Phase II of this study.

Individual data were to be listed. Data were to be summarized using suitable descriptive statistics; depending on the structure of the data, summary statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) or frequency tables may have been used.

All data were to be displayed by treatment arm if not specified otherwise.

10.1.3.1. Efficacy Analyses

The relative change (%) from baseline (day 1 prior to study drug administration at ± 1h of randomization) in oxygenation index (PaO_2 / FiO_2) in supine position at day 3, 5, 9, and 15 was to be analyzed with a linear repeated measures model with post-baseline time points as outcome variable and baseline value as explanatory variable. Deceased patients were to be included in the model with an outcome of 0 after death. Patients discharged from the ICU whose oxygenation index was no longer be assessed were to be analyzed by last observation carried forward. Treatment arm, time point, the interaction between treatment arm and time point, the interaction between baseline and time point, age, sex, and intubation status at baseline was to be included as further explanatory variables. The model was to use an unstructured covariance matrix and make

use of the Kenward-Roger degrees of freedom approximation. Least square mean differences between treatment arms and their 95% confidence interval was to be calculated and displayed for each time point separately (day 3, 5, 9, and 15), with the evaluation at day 5 reflecting the primary endpoint. If oxygenation index was to be used as the primary endpoint for a Phase III part of the study, data from both study parts were planned to be analyzed in one combined model as specified above with study part as a random effect.

Early response, late response and reaching ICU discharge alive were to be analyzed as three separate time-to-event variables. Withdrawing early from the study would have led to the patient being right-censored at the date of withdrawal provided that the reason was not an outcome of interest for the time-to-event endpoint. In order to adequately account for competing outcomes as well as potential right-censoring due to varying follow-up times, these outcomes were to be non-parametrically analyzed using Aalen-Johansen-type estimation based on a competing risks model with two absorbing states (event 1: all-cause death; event 2: early response/late response/ICU discharge respectively). The Aalen Johansen estimator estimates the expected relative number of patients (cumulative incidence function [CIF]) of the event at hand. Treatment effects were to be derived in terms of the absolute differences between the treatment arm-specific estimators evaluated at day 7:

〖Effect〗_(Y;7)=CIF_Y^A (7)- CIF_Y^B (7)

where 〖CIF〗_Y^X (7) is the Aalen-Johansen estimator evaluated at day 7 for endpoint Y∈{Death, Early Response, Late Response} within treatment group X∈{A,B}. In order to test the hypotheses

H0: 〖Effect〗_(Y;7)=0=0 vs H1: 〖Effect〗_(Y;7)≠0

Two-sided confidence intervals (CIs) were to be constructed based on the approximate normality of the estimators (Beyersmann 2012). Statistical significance was to be concluded if the two-sided 95% CI did not cover 0.

Adjustment for relevant baseline covariates (age, sex, oxygenation index and intubation status) were to be realized by cause-specific Cox models. Subdistribution hazards regression modelling were to be applied in the presence of competing risks (Fine and Gray 1999) to explore the relative covariate effects in terms of the CIF of interest. Model assumptions were to be checked using graphical diagnostics.

All-cause mortality was to be analyzed as a censored time-to-event variable with Kaplan-Meier methods. The proportion of patients still alive at 28 days was to be derived based on the product limits estimator in each treatment arm. Adjustment for relevant baseline covariates (age, sex, oxygenation index, and intubation status) was to be realized by the Cox proportional hazard model.

The individual components of the composite time-to-event endpoints early and late response and ICU discharge were to be analyzed descriptively.

Laboratory endpoints as well as the Glasgow Outcome Scale were to be analyzed descriptively by time point and treatment arm.

10.1.3.2. Safety Analyses

The occurrence of AEs was to be compared between treatment arms. Treatment-emergent AEs (TEAEs) were to be analyzed according to the number and percentage of patients who had a TEAE, as well as the number of TEAEs with the respective Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Additionally, the number and percentage of patients with TEAEs were to be further grouped by severity and causal relationship. The number and percentage of patients with SAEs and the number of SAEs were to be analyzed. Where AEs were grouped by severity or relationship, the maximum severity/relationship per patient and class of AE was to be considered.

10.1.3.3. Interim Analysis

An interim analysis was performed after the first 30 patients treated in Phase II reached at least day 15 of the study schedule to assess the clinical benefit of the treatment using the assessed clinical parameters.

10.2. Phase III

10.2.1. Sample Size Determination

A total of 180 patients (90 per arm) will be randomized in Stage 1 and up to 180 patients (90 per arm) in Stage 2. This results in 90% overall power (90% probability to either show efficacy after Stage 1 or Stage 2). The power calculation is based on an overall 2.5% one-sided alpha, Pocock's approach to account for the group-sequential design, a binding futility stop if the z-statistic is 0 or lower after the first stage and an assumed 30% 28-day mortality under Placebo and 15% 28-day mortality under IFX-1 treatment.

10.2.2. Analysis Sets

All efficacy analyses will be performed based on all randomized patients according to the intention to treat principle. Safety analyses will also be based on all randomized patients, but patients will be analyzed according to the treatment they actually receive.

10.2.3. Statistical Analyses

The SAP will be developed and finalized before the study will be unblinded. The SAP will include the exact definition of endpoints and variables to be analyzed, extensive details on the statistical analysis methods to be used together with the structure of tables and figures to be

included as end-of-text tables and figures as well as appended listings for the clinical study report. It will also describe procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and other endpoints.

Individual data will be listed. Data will be summarized using suitable descriptive statistics; depending on the structure of the data, summary statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) or frequency tables may be used.

All data will be displayed by treatment arm if not specified otherwise.

10.2.3.1. Primary Efficacy Analysis

All efficacy analyses will be performed based on all randomized patients according to the intention-to-treat principle.

The statistical study design of Phase III is a group-sequential adaptive design (two stages) with one interim analysis for stopping for futility or stopping for efficacy. The primary efficacy variable is 28-day mortality (proportion of patients deceased until day 28). The primary statistical hypotheses to be tested are:

H_0: $p_{IFX\text{-}1} = p_{Placebo}$

versus

H_1: $p_{IFX\text{-}1} < p_{Placebo}$

where $p_{IFX\text{-}1}$ is the proportion of patients deceased until day 28 in the SOC + IFX-1 treatment arm (Arm A) and $p_{Placebo}$ is the proportion of patients deceased until day 28 in the SOC + Placebo treatment arm (Arm B).

A total of 180 patients will be randomized to Arm A and Arm B using a 1:1 allocation ratio for the first stage. The interim analysis is performed after all 180 patients have been followed-up until day 28 (or died before). In case the interim analysis does not result in an early stop for efficacy or futility, 180 additional patients will be randomized in a ratio of 1:1 to Arm A and B. The maximum number of patients in the study will not exceed 360.

The group sequential design to show superiority of IFX-1 + SOC compared to SOC alone will make use of a one-sided alpha level of 2.5% and a binding futility stop and will test for superiority (lower mortality among IFX-1 treated patients). The primary statistical analysis will be based on a logistic regression model with outcome 28-day mortality and explanatory variables treatment arm (Arm B versus Arm A), age, sex (male versus female), and PaO_2 / FiO_2 at randomization.

The critical values for the interim and the final analysis are derived according to Pocock's design resulting in critical values of 2.176 for both stages. The z-statistic at each stage will be calculated as the proportion of the beta coefficient for the treatment arm effect and its standard error from the logistic regression model. The study will be stopped for futility if the z-statistic for the first stage is 0 or lower.

The z-statistics of the first and the second stage will be combined using the weighted inverse normal combination function (Bauer and Köhne 1994; Bauer and Köhne 1996). The weights are chosen as w_1= sqrt(180/360) and w_2= sqrt(1-w_1^2).

10.2.3.2. Secondary Efficacy Analyses

Secondary efficacy endpoints will only be addressed with statistical hypothesis tests if the primary endpoint is statistically significant (only after the first stage or after the second stage). Therefore, a full overall 2.5% one-sided alpha will be spent for the secondary efficacy endpoints. Multiplicity in the secondary endpoints will be addressed with the fallback method. The secondary endpoints will be evaluated using a similar logistic regression model as for the primary endpoint, where instead of the 28-day mortality (proportion of patients deceased until day 28) the following variables will be used:

1. Proportion of patients with an improvement in the provided ordinal scale at day 28 (at least one score point lower than at randomization)
2. Proportion of patients with an improvement in the provided ordinal scale at day 15 (at least one score point lower than at randomization)
3. Proportion of patients free of any renal replacement therapy within 28 days upon randomization
4. Proportion of patients developing acute kidney failure (eGFR < 15 mL/min/1.73m²) during ICU stay and at day 28

The ordering of the secondary endpoints for hypothesis testing will be as in above mentioned list. The alpha for the fallback method will be attributed to the 4 secondary endpoints in the following way 2%, 0.2%, 0.2%, and 0.1%. If the preceding hypothesis test is not significant, subsequent tests will be performed at the aforementioned alpha level. If tests are significant, the alpha is added to the subsequent hypothesis test (e.g., if the primary hypothesis test is significant and secondary endpoints 1-3 are all significant, the fourth secondary endpoint will be tested at an alpha of 2.5%; if the third secondary endpoint is not significant, the fourth secondary endpoint will be tested at an alpha of 0.1%).

The primary endpoint as well as all secondary endpoints will also be evaluated as censored time to event variables by Kaplan-Meier type methods. All time to event endpoints will also be evaluated via proportional hazards models with the explanatory variables treatment arm (Arm B versus Arm A), age, sex (male versus female), and PaO_2 / FiO_2 at randomization.

10.2.3.3. Other Efficacy Analyses

Time to First Extubation

Time to first extubation will be analyzed as a censored time to event variable. Withdrawing early from the study will lead to the patient being right-censored at the date of withdrawal provided that the reason is not an outcome of interest (extubation or death). In order to adequately account for competing outcomes as well as potential right-censoring due to varying follow-up times, the outcome will be non-parametrically analyzed using Aalen-Johansen-type estimation based on a competing risks model with two absorbing states (event 1: all-cause death; event 2: extubation). Adjustment for relevant baseline covariates (age, sex, and PaO_2 / FiO_2 at randomization) will be realized by regression modeling accounting for competing risks.

60-Day Mortality

The 60-day mortality will be derived from the above-mentioned Kaplan-Meier analysis of all-cause mortality.

Glasgow Outcome Scale

Glasgow Outcome Scale assessed at study day 60 will be analyzed via ordinal logistic regression with explanatory variables treatment arm (Arm B versus Arm A), age, sex (male versus female), and PaO_2 / FiO_2 at randomization.

Quality of Life

Quality of life will be assessed by EQ-5D at study day 60. The visual analogue scale as well as an index value based on the 5 health states (cross-walk index value using the United States value set) will be analyzed by an ANCOVA model with explanatory variables treatment arm (Arm B versus Arm A), age, sex (male versus female), and PaO_2 / FiO_2 at randomization.

10.2.3.4. Safety Analyses

The occurrence of TEAEs will be compared between treatment arms. TEAEs will be analyzed according to the number and percentage of patients who had a TEAE, as well as the number of TEAEs in total. Additionally, the number and percentage of patients with TEAEs will be further grouped by severity and causal relationship. The number and percentage of patients with serious TEAEs and AESIs and the number of serious TEAEs and AESIs will be analyzed. Where TEAEs are grouped by severity or relationship, the maximum severity/relationship per patient and class of TEAE will be considered.

10.2.3.5. Interim Analysis

The interim analysis is performed after all 180 patients in Stage 1 have been followed-up until day 28 (or died before). The study will be stopped for futility if the z-statistic of the primary

efficacy analysis is 0 or lower. The study will be stopped for efficacy if the z-statistic of the primary efficacy analysis is 2.176 or higher. If the study is not stopped for efficacy or futility, another 180 patients will be randomized in Stage 2.

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12. APPENDICES

Appendix 1 Clinical Laboratory Tests

The protocol-required laboratory assessments are detailed in Table 3 for Phase II and in Table 4 for Phase III. Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 6.1 and Section 6.2 of the protocol. In general, blood samples for safety laboratory analysis should be obtained once a day during a routine sampling (preferable in the morning). Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 3 Protocol-Required Safety Laboratory Assessments: Phase II

Assessment	Parameters	
Hematology	Hemoglobin Hematocrit Platelet count Red blood cell count Red blood cells (MCV)	White blood cell count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Coagulation parameters	APTT PT	D-Dimer
Clinical chemistry [a]	ALT (SGPT) AST (SGOT) LDH Total bilirubin Creatinine Procalcitonin	Sodium Potassium Calcium Magnesium Glucose CRP
Urinalysis (Dipstick)	PH Glucose Leucocytes Protein Blood	
Other screening tests	Troponin ISerum or urine hCG pregnancy test (as needed in women of childbearing potential)	

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring are given in Section 9.5.3. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (35% direct bilirubin) or ALT ≥3 ULN and INR >1.5 (if INR is measured), may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE.

Table 4 Protocol-Required Safety Laboratory Assessments: Phase III

Assessment	Parameters
Screening/Randomization Only (as indicated in SoA Table 2)	
Urinalysis (Dipstick)	PH Glucose Leucocytes Protein Blood
Other screening tests	Serum or urine hCG pregnancy test (in women of childbearing potential)
Screening/Randomization and Treatment (as indicated in SoA Table 2)	
Hematology	Hemoglobin Hematocrit Platelet count Red blood cell count Red blood cells (MCV) White blood cell count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Coagulation parameters	APTT PT D-Dimer
Clinical chemistry [a]	ALT (SGPT) AST (SGOT) LDH Total bilirubin CRP

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring are the same as in Phase II (listed in Section 9.5.3). All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (35% direct bilirubin) or ALT ≥3 ULN and INR >1.5 (if INR is measured), may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE.

Investigators must document their review of each laboratory safety report.

Appendix 2 Regulatory and Ethical Considerations

I. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other relevant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

II. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

III. Informed Consent Process

Obtaining of informed consent is proposed to be deferred for the ICU patients in this study or by any other legally acceptable local procedure specific for patients treated in the ICU setting (see Section 6.3).

The ICF could contain a separate section or an additional ICF may be issued that addresses the use of remaining samples for optional exploratory research. The investigator or authorized designee will explain to each patient/legal representative the objectives of the exploratory research. Patients/legal representatives will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will not provide this separate signature.

IV. Data Protection

Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient and/or the legal representative must be informed that patients' personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor will ensure that all safeguards are in place to minimize any eventual risk of breaches, and complies otherwise with the requirements of European Union (EU) General Data Protection Regulation (GDPR [EU] 2016/679). The sponsor will regularly check all procedures relevant to the processing of personal data, as to ensure privacy by design and compliance with this regulation.

V. Publication Policy

The results of this study may be published or presented at scientific meetings. Individual publications are allowed only after publication of the entire study. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of

multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

In accordance with consistent editorial practice, the sponsor supports publication of multicenter studies in their entirety and not as individual center data unless as ancillary study/data.

All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record (e.g., on ClinicalTrials.gov).

VI. Dissemination of Clinical Study Information

The sponsor will provide the relevant study protocol information in a public database (e.g., ClinicalTrials.gov, https://clinicaltrials.gov/) before or at commencement of the study. The sponsor may also provide study information for inclusion in national registries according to local regulatory requirements.

If a potential patient contacts the sponsor regarding participation in the study, the investigator agrees that the sponsor may forward the study site and contact details to the patient. Based on the inclusion and exclusion criteria for the study, the investigator will assess the suitability of the patient for enrollment into the study.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record (e.g., on ClinicalTrials.gov).

VII. Data Quality Assurance

All patient data relating to the study will be recorded on the eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

It is the responsibility of the site to comply with the protocol-defined procedures and assessments. Details about the handling of protocol deviations will be included in a separate Protocol Deviation Plan.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

VIII. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.

IX. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further IMP development

Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluation, Follow-up, and Reporting

I. Definitions

Definition of an AE
An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of IMP, whether or not considered related to the IMP. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline. Laboratory tests are considered abnormal, if – Any criterion for an SAE is fulfilled – The abnormality causes the patient to discontinue from the study treatment – The abnormality causes the patient to interrupt the study treatment or a modification of dosing – The investigator judges that the abnormality is clinically relevant and should be reported as an (S)AE in the eCRF • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Signs, symptoms, and/or clinical sequelae resulting from disease progression will be reported as AE or SAE if they fulfil the definition of an AE or SAE. The terms ‘disease progression’, ‘progressive disease’, or similar, per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.
Events <u>NOT</u> Meeting the AE Definition
• The terms ‘progressive disease’ or ‘progression of disease’ per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Definition of an SAE

If an event is not an AE according to the above definition, then it cannot be an SAE even if serious conditions are met.

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

- Results in death

- Is life-threatening

Life-threatening in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

- Required inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent disability or incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect

- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the

patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Definition of an Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined (as per ICH Topic E2A) as all noxious and unintended responses to a medicinal product related to any dose which nature or severity is not consistent with the relevant source document, i.e., current IB. When reported as serious, the unexpected adverse reaction is defined as suspected unexpected serious adverse reaction. The safety vendor is responsible for notifying suspected unexpected serious adverse reactions to concerned regulatory bodies in accordance with local regulations.

II. Procedures for Recording, Evaluation, Follow-up and Reporting of an AE, including AESIs and SAEs

Recording of AEs, including AESIs and SAEs

- When an AE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE.
- The investigator will then record all relevant information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the patient's medical records to the safety vendor in lieu of completion of the respective sections of the eCRF.
- There may be instances when copies of medical records for certain cases are requested by the safety vendor. In this case, all patient identifiers, with the exception of the patient number, must be redacted on the copies of the medical records before submission to the safety vendor.

SAE Reporting to the Safety Vendor via the eCRF

- The safety vendor for this study is IQVIA Pharmacovigilance and is responsible for SAE processing and reporting.
- The primary mechanism for reporting an SAE to the safety vendor will be the eCRF.
- Investigators and other site personnel must report those SAEs that are outlined under Section 9.2 within 24 hours of becoming aware. The same applies for follow-up information on SAEs.
- A paper SAE reporting form needs to be completed by the investigator or other relevant site staff, signed by the investigator, and faxed to +353 1 809 9501 or QLS_IFX1@iqvia.com.

Assessment of Intensity for AEs, including AESIs and SAEs

The investigator will make an assessment of intensity for each AE reported during the study and assign it to 1 of the following categories (NCI CTCAE v5.0):

- Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 (Moderate): minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*
- Grade 3 (Severe/medically relevant but not immediately life-threatening); hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- Grade 4 (Life-threatening): Life-threatening consequences; urgent intervention indicated
- Grade 5 (Death): Death related to AE

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Assessment of Causality of AEs, including AESIs and SAEs

- The investigator is obligated to assess the relationship between IMP and each occurrence of each AE.
- A ‘reasonable possibility‘ of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered, investigated, and reported.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the safety vendor. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the safety vendor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs, including AESIs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or the safety vendor to elucidate the nature and/or causality of the AE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • In case of persisting SAEs, follow-up must continue until the AEs have resolved to grade ≤1 or baseline or are deemed irreversible by the investigator. • If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the safety vendor with a copy of any post-mortem findings including histopathology, if any would become available. • The investigator will submit any updated SAE data to the safety vendor within 24 hours of receipt of the information.

III. Special Considerations for Assessment of Adverse Events in an ICU Setting

Due to the severity of disease of the patient population entering this study, numerous problems, signs, and symptoms deviating from normal will be seen during the course of the study. These will not necessarily constitute a reportable AE unless they require significant intervention, lead to discontinuation of blinded study drug, or are considered to be of concern in the investigator's clinical judgement. Similarly, it is preferred to receive documentation of the underlying condition rather than the resulting sign (e.g., 'agitation' rather than 'self-extubation').

In clinical studies in intensive care, deviations, e.g., in laboratory values or temporary changes in arterial blood pressure, are to be expected frequently. Clinical judgement should be applied in determining which deviations should be reported as an AE in the sense of an "untoward medical occurrence" and which deviations should be considered usual and expected findings in this setting.

It must be noted that clinically relevant laboratory deterioration as assessed by the investigator must be documented in the respective eCRF section. However, it is preferred to document the condition or disease underlying the aberrant laboratory value (e.g., renal failure rather than hyperkalemia) rather than the laboratory value only.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant, and thus constitutes an AE.

Appendix 4 Contraceptive Guidance and Collections of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

3. Postmenopausal female:
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male Patients

Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the study and until 3 months after last dose of IFX-1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 5 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration [during the protocol-defined time frame].

Female Patients

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception (from the day of study medication initiation throughout the study period and up to 3 months for IFX-1 after the last dose of study medication) consistently and correctly as described in Table 5. During the treatment period of the study conception is assumed to be precluded by the severe clinical conditions for included patients and applicability of sexual abstinence as a contraceptive method can be assessed by the investigator in case a patient confirmation cannot be gained.

Table 5 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] (failure rate of <1% per year when used consistently and correctly)
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: [b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation: [b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion

Vasectomized partner: A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.
b Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 3 months after the last dose of IFX-1.

Pregnancy Testing

WOCBP should only be included after a negative serum or urine pregnancy test.

Collection of Pregnancy Information

Male Patients with Partners who Become Pregnant

The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive IFX-1.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients who Become Pregnant

The investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and

submitted to the sponsor within 24 hours of learning of a patient's pregnancy. The patient will be followed at least monthly to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the IMP by the investigator will be reported to the safety vendor as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating in the study will discontinue IMP.

Appendix 5 Treatment Modification Guidelines

Table 6 Dose Modification and Toxicity Management Guidelines for Infusion Reactions Associated with IFX-1

Grade	Treatment	Premedication at Subsequent Dosing
mild Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
moderate Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Patient may be premedicated 1.5 h (± 30 minutes) prior to infusion of IMP with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
severe Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately.	No subsequent dosing

life-threatening: Life-threatening; pressor or ventilator support indicated	Patient is permanently discontinued from further study drug treatment.	

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov.

Appendix 6 Conversion Tables for PaO_2 / FiO_2 Ratio

The following conversion tables should be used if a blood gas analysis is not available.

Estimating PaO_2 from a measured SO_2

SO_2	Calculated PaO_2 (mmHg)	SO_2	Calculated PaO_2 (mmHg)	SO_2	Calculated PaO_2 (mmHg)
80	44	87	53	94	73
81	45	88	55	95	79
82	46	89	57	96	86
83	47	90	60	97	96
84	49	91	62	98	112
85	50	92	65	99	145
86	52	93	69		

Estimating FiO_2 with known O_2 Application Flow

Method	O_2-Flow (l/min)	Estimated FiO_2 (%)
Nasal O_2 Tube Nasal Prong	1 2 3 4 5 6	24 28 32 36 40 44
Nasopharyngeal Catheter	4 5 6	40 50 60
Oxygen Mask	5 6–7 7–8	40 50 60
Oxygen Mask with Reservoir	6 7 8 9 10	60 70 80 90 95

Appendix 7 Ordinal Scale

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Appendix 8 New York Heart Association (NYHA) Classification

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath)
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Appendix 9 Child-Pugh Classification

Category	Hepatic Function	Score
Child-Pugh A	Good	5 to 6 points
Child-Pugh B	Moderately impaired	7 to 9 points
Child-Pugh C	Advanced hepatic dysfunction	10 to 15 points

	1 point	2 points	3 points
Encephalopathy:	None	Grade 1 and 2	Grade 3 and 4
Ascites:	None	Slight	Moderate
Bilirubin:	< 2 mg/mL	2 to 3 mg/mL	> 3 mg/mL
Albumin:	> 3.5mg/mL	2.8 to 3.5mg/mL	< 2.8mg/mL
Prothrombin Time OR INR	< 4 sec < 1.7	4 to 6 sec 1.7 to 2.2	> 6 sec > 2.2

Appendix 10 Special Considerations for Assessment of Prior and Concomitant Medications

A complete record of all prior and concomitant drugs (but excluding nutritional and volume therapy, electrolyte support, vitamins, NSAIDs, and supportive therapies such as artificial tears, ointments, stool softeners/laxatives, etc.) will be maintained in the eCRF for each participant, beginning at baseline and continuing until day 28 or hospital discharge (whatever occurs earlier).

In addition, a complete record of all steroid and antibiotic therapy and any therapy (drugs, specific treatments, etc.) associated with or used in the assessment or treatment of an adverse event will be documented for the duration of the study.

The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, and indication.

All medications administered within 7 days before randomization should be recorded with generic name, route of administration, start date, stop date, and indication.

Appendix 11 Protocol Version History

VERSION 2.0: 30 JULY 2020

This protocol version is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU.

Overall Rationale for Version 2.0

After completion of the explorative Phase II (30 patients) of this adaptive study, the Expert Committee has recommended on proceeding to a confirmatory Phase III study based on interim analysis results suggesting that multi-organ failure is the leading cause of death for critically ill COVID-19 patients on mechanical ventilation. According to the findings from the preliminary interim analysis and after discussion with the Expert Committee, the Phase III design was established. In particular, the primary endpoint was modified to all-cause 28-day mortality, and secondary endpoints were adapted.

Major updates made in Protocol Version 2.0 for Phase III of the study include the addition of information on the updated study design, endpoints, conduct, treatment administration, and statistical methods, as described in the table below.

Table 7 Protocol Version History: Major Updates to Phase III

Section(s)	Description of Change	Brief Rationale
	Overall	Where applicable, protocol sections were separated into subsections for Phase II and Phase III. This version includes study design elements applicable to Phase III of the study.
1, 4.1.1	Primary study objective updated	To align with new primary endpoint and primary analysis for Phase III
1, 10.2	Number of sites increased from 6 in 3 countries to approximately 25 in 7 countries	Given the currently unpredictable epidemiology of COVID-19, additional sites in more countries will improve the ability to enroll the study in a timely manner.
1, 5.2, 10.2	Number of patients to be enrolled in Phase III increased from an estimated 100 patients to up to 360 patients	The sample size was changed to ensure a sufficient sample size to yield an overall 90% power to show superiority of IFX-1 over SOC for the endpoint of 28-day all-cause mortality.
1, 5	Added details on the study design for Phase III	Phase III will be a double-blind, placebo-controlled study in a group-sequential adaptive design (two stages) with one interim analysis for stopping for futility or stopping for efficacy in order to fulfill regulatory requirements for a confirmatory study.
1, 5, 7.2.1	The maximum number of IMP doses to be administered was decreased from 7 in Phase II to 6 in Phase III.	The additional IMP administration between day 11 and 13 that was given in Phase II was removed in Phase III because experience from Phase II provided no evidence of the benefit of an additional dose.
1, 6	Clarified that all study patients are enrolled using a deferred consent.	This was the same approach used in Phase II, due to the likelihood that a large proportion of patients or no patient will be unable to provide informed consent before the beginning of the

Section(s)	Description of Change	Brief Rationale
		study. In Phase III, only patients requiring mechanical ventilation are eligible.
1, 6.2	Added inclusion and exclusion criteria for Phase III	Only patients on mechanical ventilation are enrolled in Phase III because the Phase II preliminary interim results suggest that these patients benefit the most from IFX-1 treatment.
1	Expected study duration was increased by approximately 6 months	The increased sample size for Phase III was taken into consideration.
1, 4.2.2	Primary endpoint for Phase III was changed to all-cause mortality at day 28.	Based on the interim analysis results of lower mortality rates in the IFX-1 arm compared with the BSC arm, the primary endpoint chosen for Phase III is 28-day all-cause mortality, which is an accepted regulatory primary endpoint for critical care studies.
1, 4.2.2, Appendix 7	Ordinal scale was added as a secondary endpoint	The ordinal scale is commonly used in COVID-19 trials to assess patient's clinical status.
1, 4.2.2	EQ-5D was added as a secondary endpoint	EQ-5D is a commonly used patient-reported outcome in confirmatory studies and a recommended tool for COVID-19 studies by several regulatory bodies.
1, 4.2.2	Additional secondary and other endpoints were added for Phase III	These endpoints were added based on interim analysis results from Phase II.
1, 10.2	Statistical methods were added for Phase III	To reflect the updated study design
2	Schedule of Assessments was added for Phase III	To reflect the updated study design
3	Background and dose justification updated	To reflect current understanding of SARS-CoV-2, COVID-19, and new data from interim analysis of Phase II.
5.1.1, 5.1.2, 7.1, 7.2	Text updated to reflect that Phase III will be double-blinded and placebo-controlled; Figure 2 added to show IMP administrations in Phase III	To reflect the updated study design
5.5	Added section on iDMC	Includes information on how and by whom the interim analysis during Phase III will be performed
5.5.2 and subsections	Definitions of end of treatment and end of study were added for Phase III	Phase III included 1 less follow-up visit than Phase II, since follow-up of patients discharged from hospital in the COVID-19 situation is expected to be difficult and a longer follow up would lead to a high proportion of missing information.
7.3, 7.4, 8.2.1, Appendix 10	Reporting of prior and concomitant medications will follow special considerations.	Requirements for recording of prior and concomitant medications were simplified for the ICU setting.
7.4.1	Additional prohibited concomitant medications added	To reflect the exclusion criteria for Phase III
8.2	Study assessments and procedures are added for Phase III.	Efficacy and safety assessments were simplified for the ICU setting, based on clinical experience derived from Phase II of the study.
9, Appendix 3	AE collection and reporting requirements updated	AE collection and reporting were simplified for the ICU setting, based on clinical experience derived from Phase II of the study
9.8, Appendix 2	Updated some text on regulatory and ethical considerations	Phase III of the study will be conducted at US sites, so IRB is added where IEC is mentioned. Informed consent and data

Section(s)	Description of Change	Brief Rationale
		protection language updated to adapt to ICU setting. Storage of records updated to 15 years. Other minor updates are made.
11	Reference list updated	To reflect updated Background section
Appendix 8	Added NYHA Classification scale	For reference
Appendix 9	Added Child-Pugh Classification scale	For reference
Appendix 11	Added protocol version history	To reflect changes to current protocol version.

Additional major updates made in Protocol Version 2.0 that were retrospectively applied to Phase II mainly include text that was simplified or adapted to an ICU setting, as described in the table below.

Table 8 Protocol Version History: Major Updates to Phase II

Section(s)	Description of Change	Brief Rationale
	Overall	Where applicable, protocol sections were separated into subsections for Phase II and Phase III. Because Phase II is now completed, all information relevant only to Phase II of the study has been changed to past tense and font color changed to grey. "Subject(s)" changed to "Patient(s)" throughout to reflect the COVID-19 diseased population, and not healthy subjects, in the trial.
5.5.1.3	Clarification made	Removed "In such a case the EOS visit information will be added to the EOT visit information.", as this language was unclear.
5.5.1.4	Text on patients lost to follow-up updated	Text adapted to an ICU setting
6.4	Revised definition of screening failures	Text adapted to an ICU setting
6.5	Removed dietary requirements	Text adapted to an ICU setting
7.2, 7.3, 9.2.1, 9.6, Appendix 5	"Infusion-related reactions" was changed to "infusion reactions"	"Infusion reactions" is more a more accurate description of these events.
7.2.4	Removed "disease progression"	Text adapted to an ICU setting
7.3	Removed "in the treatment facility"	Text adapted to an ICU setting
7.4	Requirements for recording of prior and concomitant medications were revised	Requirements were simplified and adapted to an ICU setting
9.1	Text on frequency of collection and reporting revised	AESIs were included in the specified AEs to be reported until 30 days following the last IFX-1 administration. SAEs was moved to the first bullet; bullets 1 and 2 combined since they follow the same timelines
9.1.1, 9.1.1.1, 9.1.2	Headings renamed and text updated accordingly	Removed visit names that were used only in Phase II, to make the text applicable to Phase III as well.
9.1.1.1, 9.2.1	"Death" was revised to "Events with fatal outcome"	Death is not an SAE, but the outcome of an SAE.

Section(s)	Description of Change	Brief Rationale
9.2.2	"Not Related" was changed to "Unrelated"	Harmonization of terminology

inflaRx

CONFIDENTIAL

CLINICAL STUDY PROTOCOL

A PRAGMATIC ADAPTIVE RANDOMIZED CONTROLLED PHASE II/III MULTICENTER STUDY OF IFX-1 IN PATIENTS WITH SEVERE COVID-19 PNEUMONIA –– "PANAMO"

Protocol Number:	IFX-1-P2.9
Compound:	IFX-1
Phase:	II - III
Indication:	Severe pneumonia in context of COVID-19
EudraCT Number:	2020-001335-28
Sponsor Name and Address:	InflaRx GmbH Winzerlaer Strasse 2 07745 Jena, Germany
Version and Date:	Version 4.0, 12 May 2021

PROTOCOL SIGNATURES

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Protocol Number:	IFX-1-P2.9
Title:	A pragmatic adaptive randomized controlled phase II/III multicenter study of IFX-1 in patients with severe COVID-19 pneumonia --- "PANAMO"

Sponsor Signatory:

_____ _____

Date

InflaRx GmbH
Fraunhofer Strasse 22
82152 Planegg / Martinsried
Germany

Medical monitor name and contact information will be provided separately.

Statistician:

_____ _____

Date

Signature of Coordinating Investigator

Protocol Number:	IFX-1-P2.9
Title:	A pragmatic adaptive randomized controlled phase II/III multicenter study of IFX-1 in patients with severe COVID-19 pneumonia --- "PANAMO"

Herewith I declare that I have read and understood the present protocol and agree to honor each part of it. By signing this study protocol, I agree to conduct the clinical study, following approval by an Ethics Committee, in accordance with the study protocol, the current International Council for Harmonization Guidelines for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all the subjects enrolled in the study by my site will be treated, observed, and documented in accordance with this protocol. I will ensure that all persons assisting with the study under my supervision are adequately informed about the protocol, the investigational product, and their duties.

Alexander Vlaar, MD, PhD Coordinating Investigator	Date

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The Netherlands

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ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AMC	Amsterdam Medical Center
AMG	German Medicines Act (in German: “Arzneimittelgesetz”)
aPTT/APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BSC	Best supportive care
BDB	Beijing Deferengui Biotech
C5a	Complement factor 5a
CFR	Code of Federal Regulations
CI	Confidence interval
CIF	Cumulative incidence function
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease-19
CRO	Contract Research Organization
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EC	Expert committee
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EU	European Union
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
EQ-5D	EuroQol 5-D (quality of life assessment tool)
FAS	Full analysis set
FSH	Follicle-stimulating hormone
FUV	Follow-up visit

GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HR	Hazard ratio
HRT	Hormone replacement therapy
HS	Hidradenitis suppurativa
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IgG4	Immunoglobulin G4
IMP	Investigational Medicinal Product
INR	International normalized ratio
IRB	Institutional Review Board
iSMB	Independent Safety Monitoring Board
IV	Intravenous
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PaO_2 / FiO_2	Oxygenation index
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PE	Pulmonary embolism
PK	Pharmacokinetic
PT	Prothrombin time
PTT	Partial thromboplastin time
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan

SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SoA	Schedule of assessments
SOC	Standard of care
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
USA	United States of America
VTE	Venous thromboembolism
WHO	World Health Organization
WMO	The Dutch Medical Research Involving Human Subjects Act (in Dutch: Wet medisch-wetenschappelijk onderzoek met mensen)
WOCBP	Women of childbearing potential

1. SYNOPSIS

Title of Study:

A PRAGMATIC ADAPTIVE RANDOMIZED, CONTROLLED PHASE II/III MULTICENTER STUDY OF IFX-1 IN PATIENTS WITH SEVERE COVID-19 PNEUMONIA --- "PANAMO"

Protocol/Study Number: IFX-1-P2.9

EudraCT Number: 2020-001335-28

Type of Study:	**Indication:**
Phase II/III Study	Severe pneumonia in context of Coronavirus Disease-19 (COVID-19)

Sponsor: InflaRx GmbH, Winzerlaer Strasse 2, 07745 Jena, Germany

Coordinating Investigator: Alexander Vlaar, MD, PhD, Amsterdam University Medical Center, The Netherlands

Study Site(s): Approximately 60 sites in approximately 10 countries in Europe, Russia, South Africa, United States of America (USA), and Latin America

Phase of Development: II/III

Objectives:

Primary Objectives:

Phase II: To explore the effect of IFX-1 on COVID-19 related severe pneumonia (hypothesis generating)

Phase III: To demonstrate the efficacy of IFX-1 to improve survival outcomes of severe COVID-19 pneumonia (confirmative)

Secondary Objectives:

Phase II and Phase III

- To assess and define other parameters of efficacy
- To assess the safety of IFX-1

Methodology:

This is a pragmatic, adaptive, randomized, multicenter phase II/III study evaluating IFX-1 for the treatment of COVID-19 related severe pneumonia. The study consists of two parts: Phase II, an open-label, randomized, 2-arm phase evaluating best supportive care (BSC) + IFX-1 (Arm A) and BSC alone (Arm B); and Phase III, a double-blind, placebo-controlled, randomized phase comparing standard of care (SOC) + IFX-1 (Arm A) versus SOC + placebo-to-match (Arm B). The SOC includes venous thromboembolism prophylaxis at a minimum,

and may include other international and country-specific recommended treatments for COVID-19 per the locally adopted treatment recommendations.

At the time of writing of Protocol Version 2.0, Phase II of the study has been completed and 30 patients have been treated. A preliminary interim analysis has been performed to assess the clinical benefit of the treatment using the assessed clinical parameters. An expert committee has monitored safety and the supported re-definition of relevant clinical endpoint(s) for Phase III.

In Phase II, patients in Arm A were treated with a maximum of 7 intravenous (IV) doses of IFX-1 800 mg over a period of 29 days. The first 5 treatments at days 1, 2, 4, 8, and 15 were administered to all patients. Treatment at day 22 was only administered in the event that a patient had not been extubated and discharged from the intensive care unit (ICU). In case a patient's clinical situation worsened after day 8, although an initial clinical benefit was observed, one additional administration of 800 mg IFX-1 between day 11 and 13 could have been given at investigator discretion. Loss of clinical benefit could, in this situation, relate to the exceptionally high complement factor 5a (C5a) levels observed in some cases of COVID-19 related pneumonia and associated shortened IFX-1 half-life.

Phase III of the study will randomize up to 400 patients with one interim analysis for stopping for futility. A total of 180 patients are planned to be randomized into Arm A and Arm B using a 1:1 allocation ratio for the first stage; based on results of the interim analysis, up to an additional 180 patients are planned to be randomized using the same allocation ratio for the second stage. For patients randomized in error (screening failures) and patients for whom consent is withdrawn within 48 hours after randomization, additional patients will be randomized.

In Phase III, patients will be treated with a maximum of 6 IV doses of IFX-1 800 mg (Arm A) or placebo (Arm B) at days 1, 2, 4, 8, 15, and 22, as long as the patient is still in the hospital (even if discharged from the ICU).

Patients will be assessed for quality of life using the EuroQol-5D (EQ-5D).

Patients will be followed for survival and their clinical status assessed by the Glasgow Outcome Scale.

Number of Patients:

Phase II: 30 patients (15 arm A+ 15 arm B)

Phase III: Total of 180 patients (approximately 90 per arm) in Stage 1 and 180 patients (approximately 90 per arm) in Stage 2 are planned. The assumed rate for randomization of additional patients, i.e. patients randomized in error (screening failures) and patients for whom consent is withdrawn within 48 hours after randomization, is 10%. The planned maximum number of patients in the study is 400, 200 patients per treatment arm. The sample size ensures 90% power to show superiority of IFX-1 for the primary endpoint of 28-day all-cause mortality. Sample size calculations were based on the assumption that IFX-1 can reduce a 30% mortality under SOC by 50% to a mortality of 15% and that at least 360 patients are evaluable for the primary endpoint for the final analysis.

Study Population:

Study patients are enrolled into the study using a deferred consent procedure or another legally acceptable local consent procedure in this special ICU situation.

Phase II

Key inclusion criteria for Phase II of the study included the following: patients must have been at least 18 years of age or older with clinically evident or otherwise confirmed severe pneumonia, oxygenation index (PaO_2 / FiO_2) at time of enrollment of ≤ 250 and ≥ 100, and had Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection confirmation at screening and at enrollment.

Key exclusion criteria for Phase II of the study included the following: PaO_2 / FiO_2 ≤ 99 or ≥ 250 at screening, intubated > 48h at time of enrollment, demonstrated an improvement in past 24h prior to enrollment in oxygenation and ventilation/support parameters, known history of chronic dialysis or received renal replacement therapy in past 14 days, and history of chronic obstructive pulmonary disease (COPD).

All inclusion and exclusion criteria are listed for Phase II in Section 6.1.

Phase III

Patients must meet all the following criteria at randomization to be enrolled into Phase III of the study:

1. At least 18 years of age or older
2. Patient on invasive mechanical ventilation (but not more than 48 h post intubation at time point of first IMP administration)
3. Patients with a PaO_2 / FiO_2 ratio of < 200 and > 60 at randomization (one representative measurement within 6h before randomization)
4. SARS-CoV-2 infection confirmation (tested positive in last 14 days before randomization with locally available test system)

Patients who fulfill any of the following criteria at randomization are not eligible to participate in Phase III of the study:

1. Intubated > 48 h at time point of first IMP administration
2. Expected stop of invasive ventilation or expected extubation in the next 24h without additional intervention according to judgment of the investigator
3. Known history of chronic dialysis OR received renal replacement therapy in past 14 days OR anticipated to receive renal replacement therapy within 24h after randomization
4. Known history of progressed COPD as evidenced by use of daily maintenance treatment with long-acting bronchodilators or inhaled/oral corticosteroids for > 2 months
5. Treatment of COVID-19 with investigational antibody treatment(s) which are not approved or not included in locally adopted treatment guidelines (e.g., World Health Organization [WHO] guidance, National Institutes of Health [NIH] COVID-19 treatment

guidelines) for this indication in the past 7 days (Note: Antibody treatment[s] given within past 7 days for pre-existing diseases, other than COVID-19, are allowed.)

6. At time point of randomization, treatment of COVID-19 with investigational treatments which are not approved or not included in locally adopted treatment guidelines for this indication (e.g., WHO guidance, NIH COVID-19 treatment guidelines), including SARS-CoV-2 multiplication inhibitor(s) or immunomodulator(s). (Note: If a locally adopted treatment guideline recommends drugs such as remdesivir, dexamethasone, or anticoagulation, this would be allowed. Adopted guidelines and updates must be documented at study initiation and throughout the conduct of the study.)
7. Received cytokine adsorption therapy in past 3 days
8. Known hypersensitivity to IFX-1 or any other ingredient of the study medication
9. Serum or urine pregnancy test positive before randomization (required for women of childbearing potential)
10. Received organ or bone marrow transplantation in past 3 months
11. Known cardio-pulmonary mechanical resuscitation in past 14 days
12. Patient moribund or expected to die in next 24h according to the judgment of the investigator
13. Known to have received anti-cancer therapy for hemato-oncological disease in past 4 weeks OR known to have active malignant disease at time point of randomization
14. Known severe congestive heart failure (corresponding to e.g. New York Heart Association [NYHA] Class III-IV, left ventricular ejection fraction <40%; see Appendix 8)
15. Known history of chronic liver disease (Child-Pugh B or C; see Appendix 11)
16. Participating in or has participated in other investigational interventional studies (drug or device) within the last 7 days before randomization

Test Product, Dose, and Mode of Administration:

Phase II

In Arm A, patients received BSC + IFX-1. IFX-1 was to be administered as a 30-60 minute IV infusion as follows: 800 mg on days 1, 2, 4, 8, and 15 and, if not extubated or in weaning process in case of tracheostomy, may have received an additional 800 mg dose at day 22. IFX-1 treatment was to be ceased if signs of unacceptable toxicity or intolerability occurred. In case a patient's clinical situation worsened after day 8, although an initial clinical benefit was observed, one additional administration of 800 mg IFX-1 between day 11 and 13 may have been given at investigator discretion.

Phase III

In Arm A, patients will receive SOC + IFX-1. IFX-1 will be administered as a 30-60-minute IV infusion as follows: 800 mg at days 1, 2, 4, 8, 15, and 22, as long as the patient is still in the hospital (even if discharged from the ICU). IFX-1 treatment shall be ceased if signs of unacceptable toxicity or intolerability occur.

Reference Therapy, Dose, and Mode of Administration:

Phase II

In Arm B, patients received BSC alone.

Phase III

In Arm B, patients will receive SOC + Placebo in the same schedule as described for Arm A. SOC treatment start and stop is not defined by the protocol and can start at any time. SOC treatment will be given according to investigator's discretion.

Expected Study Duration:

First patient first visit: March 2020 (Phase II)

Last patient last follow-up visit: August 2021 (Phase III)

Criteria for Evaluation

Phase II

Primary Endpoint:

The primary endpoint was the relative change (%) from baseline (day 1 prior to study drug administration at ± 1h of randomization) in oxygenation index (PaO_2 / FiO_2) in supine position at day 5.

Secondary endpoints included the number of patients (%) achieving an early and late response, relative change (%) from baseline (day 1 prior to study drug administration at ± 1h of randomization) in PaO_2 / FiO_2 in supine position at day 3, 7, 9, and 11, all cause 28-day mortality (%), and frequency, severity, and relatedness to study drug of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Further details on secondary and other endpoints for Phase II are provided in Section 4.2.1.

Phase III

Primary Endpoint:

- 28-day all-cause mortality

Secondary Endpoints:

- 60-day all-cause mortality (proportion of patients deceased until Day 60)
- Proportion of patients with an improvement in the 8-point ordinal scale (Appendix 7) (day 15, day 28)
- Proportion of patients developing acute kidney failure (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73m², assessed by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation requiring race information) during ICU stay and at day 28

- Proportion of patients free of any renal replacement therapy within 28 days upon randomization
- Frequency, severity, and relatedness to study drug of serious and non-serious TEAEs

Other Endpoints:

- Time to first extubation
- Proportion of patients achieving 8-point ordinal scale score 3 or below (patients alive and free of respiratory failure) at day 15 and day 28
- Glasgow Outcome Scale score assessed at study day 60
- Quality of life assessed by EQ-5D at study day 60.

Statistical Methods:

Phase II

For efficacy analyses, the relative change (%) from baseline (day 1 prior to study drug administration at ± 1h of randomization) in oxygenation index (PaO_2 / FiO_2) in supine position at day 3, 5, 9, and 15 was to be analyzed with a linear repeated measures model with post-baseline time points as outcome variables and baseline value as an explanatory variable. Least square mean differences between treatment arms and their 95% confidence interval (CI) were to be calculated and displayed for each time point separately (day 3, 5, 9 and 15), with the evaluation at day 5 reflecting the primary endpoint. Early response, late response, and reaching ICU discharge alive were to be analyzed as three separate time-to-event variables. All-cause mortality was to be analyzed as a censored time-to-event variable with Kaplan-Meier methods. Laboratory endpoints were to be analyzed descriptively by time point and treatment arm. Glasgow Outcome Scale was to be analyzed by ordinal regression analysis.

For safety analyses, the occurrence of adverse events (AEs) was to be compared between treatment arms. The number and percentage of patients with SAEs was to be analyzed.

Further details of statistical methods for Phase II are provided in Section 10.1.

Phase III

Efficacy:

The primary statistical analysis will be based on all randomized patients except patients randomized in error (reason for early termination documented as “Randomized by mistake” in the eCRF) who did not get IMP treatment. For patients randomized in error (screening failures) and patients for whom consent is withdrawn within 48 hours after randomization, additional patients will be randomized.

The primary efficacy variable is 28-day mortality (proportion of patients deceased until day 28).

The planned maximum number of patients in the study is 400. Up to 200 patients are planned to be randomized to Arm A and Arm B using a 1:1 allocation ratio for the first and for the

second stage each. The sample size calculation is based on an assumed rate of about 10% for additional patient randomization. A total of 180 patients (approximately 90 per arm) in Stage 1 and up to 180 patients (approximately 90 per arm) in Stage 2 are planned to be analyzed in a combined fashion for the final efficacy analyses. This results in 90% overall power to show superiority of IFX-1. The power calculation is based on an overall 2.5% one-sided alpha and an assumed 30% 28-day mortality under Placebo and 15% 28-day mortality under IFX-1 treatment.

The interim analysis is performed after 180 patients, not counting patients being randomized in error, have been followed-up until day 28 (or died before). In case the interim analysis does not result in an early stop for futility, up to 180 additional patients are planned to be randomized in a ratio of 1:1 into Arm A and B.

The primary analysis of IFX-1 + SOC compared to SOC alone will make use of a one-sided alpha level of 2.5% and will test for superiority (lower mortality among IFX-1 treated patients). The primary statistical analysis will be based on a Cox proportional hazards regression model with outcome all-cause mortality as a censored time-to-event variable and explanatory variables randomized treatment arm (Arm B versus Arm A) and age. The primary statistical analysis will be based on all randomized patients except patients randomized in error (screening failures). For the primary analysis, all-cause mortality will be censored at day 28 for subjects who died after day 28 or who have more than 28 days follow-up alive.

The z-statistic for the interim and final analysis will be calculated as the proportion of the beta coefficient for the treatment arm effect and its standard error from the Cox proportional hazards regression model. The study will be stopped for futility if the z-statistic for the first stage is 0 or lower.

The first secondary efficacy endpoint will only be addressed with statistical hypothesis tests if the primary endpoint is statistically significant, using the full overall 2.5% one-sided alpha. If the first secondary endpoint is also statistically significant, the full 2.5% one-sided alpha will be passed to the 4 remaining secondary endpoints. Multiplicity in the secondary endpoints will be addressed with the fallback method. 60-day mortality will be analyzed similar to 28-day mortality, and the other secondary endpoints will be evaluated using a logistic regression model with the explanatory variables randomized treatment arm (Arm B versus Arm A) and age:

1. 60-day all-cause mortality
2. Proportion of patients with an improvement in the provided 8-point ordinal scale at day 15 (at least one score point lower than at randomization)
3. Proportion of patients with an improvement in the provided 8-point ordinal scale at day 28 (at least one score point lower than at randomization)
4. Proportion of patients developing acute kidney failure (eGFR < 15 mL/min/1.73m²) during ICU stay and at day 28
5. Proportion of patients free of any renal replacement therapy within 28 days upon randomization

The ordering of the secondary endpoints 2 to 5 for hypothesis testing will be as in above mentioned list. The full 2.5% one-sided alpha for the fallback method will be attributed to

these 4 secondary endpoints in the following way: 2%, 0.2%, 0.2%, and 0.1%. If the preceding hypothesis test is not significant, subsequent tests will be performed at the aforementioned alpha level. If tests are significant, the alpha is added to the subsequent hypothesis test (e.g., if the primary hypothesis test is significant and secondary endpoints 1-4 are all significant, the fifth secondary endpoint will be tested at an alpha of 2.5%; if the fourth secondary endpoint is not significant, the fifth secondary endpoint will be tested at an alpha of 0.1%).

The primary endpoint as well as all secondary endpoints will also be evaluated as censored time to event variables by Kaplan-Meier type methods.

Safety:

The occurrence of TEAEs will be compared between treatment arms. TEAEs will be analyzed according to the number and percentage of patients who had a TEAE, as well as the number of TEAEs in total. Additionally, the number and percentage of patients with TEAEs will be further grouped by severity and causal relationship. The number and percentage of patients with serious TEAEs and adverse events of special interest (AESIs) and the total number of serious TEAEs and AESIs will be analyzed. Where TEAEs are grouped by severity or relationship, the maximum severity/relationship per patient and class of TEAE will be considered.

Interim Analysis:

The interim analysis is performed after 180 patients, not counting patients being randomized in error, in Stage 1 have been followed-up until day 28 (or died before). The study will be stopped for futility if the z-statistic of the primary efficacy analysis is 0 or lower. If the study is not stopped for futility, another up to 180 patients will be randomized in Stage 2. Depending on the number of patients meeting criteria for additional randomization, more than 360 patients will be randomized but not more than a total of 400.

2. SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments: Phase II

	Screening Period	Treatment Period (Maximum 4 Weeks)												Follow-up Period (2 Months)(Telephone)	
														EOT = FUV 1	EOS= FUV 2
	Days -2 – 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7	Day 8	Day 9	Day 11	Day 13	Day 15	Day 22	Day 29/ Discharge	28 days after last IFX-1 treatment	28 days after FUV 1
Deferred Informed consent[a]	X															
Inclusion/exclusion criteria	X															
Demographics, medical/disease history, prior medications	X															
Disease/response assessments[b]	X			X		X	X		X	X	X	X	X	X		
Imaging[c]	X					X			X			X		X		
Concomitant disease	X															
Concomitant medications	X	X		X			X		X			X	X			
Blood sample for plasma complement and PK assessment[d]		X	X					X						X		
IV administration of IFX-1[e]		**X**	**X**		**X**			**X**		**(x)**		**X**	**(x)**			
Safety Assessments																
Weight	X				X			X				X	X	X		
Height	X															
Physical examination	X				X			X				X	X	X		
Safety laboratory test[f]		X	X		X			X		(x)		X	X	X		

Pregnancy test[g]	X													X		
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X												X			
Survival status								X					X	X	X	X

CT = computed tomography; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; FUV = follow-up visit; IMP = investigational medicinal product; IV = intravenous; MRI = magnetic resonance imaging; PK = pharmacokinetic

a Obtaining of informed consent was to be deferred for the ICU patients (see Section 6.3).

b Disease/response assessments included evaluation of lung function and evaluation of early and late response (see Section 8.1.2).

c Imaging was to be performed by X-ray or CT scan or MRI, per investigator decision. Once the imaging choice was made, subsequent assessments should have been made using the same modality whenever possible. Imaging either at day 29 or day of discharge ± 3 days.

d Blood samples were to be collected for measurement of plasma concentrations and C3a and C5a of IFX-1 **before administration of IMP** (see Section 8.1.4), if possible.

e The first 5 treatments of IFX-1 at day 1, 2, 4, 8, and 15 were to be administered to all patients randomized to Arm A. Treatment at day 22 was only to be administered in the event that a patient had not been extubated and discharged from ICU. In case a patient's clinical situation would worsen after day 8, although an initial clinical benefit was observed, one additional administration of IFX-1 between day 11 and 13 could have been given at investigator discretion, represented as (x) above.

f Safety laboratory tests included hematology, coagulation parameters, chemistry, urinalysis, and other screening tests (see Table 3). Blood samples for safety laboratory analysis should have been obtained after vital signs assessments were performed, but **before administration of IMP**.

g Blood samples for serum pregnancy testing were to be collected only for women of childbearing potential.

h Core body temperature, heart rate, respiratory rate, and blood pressure (diastolic and systolic) were to be assessed at each visit at pre-dose, and H0+1h, where H0 is the beginning of IFX 1 administration, on the days of IMP administration and at further time points whenever medically indicated. Vital signs were to be measured in a supine position (after a rest of at least 1h in case of position switch from prone position), preferably in the morning.

Table 2 Schedule of Assessments: Phase III

	Screening/ Randomization	Treatment Period IMP administration and assessments as long as in ICU / Hospital									Follow-up Period (Telephone possible)	
		Week 1			Week2	Week 3	Week 4	Week 5	Any time		FUV	
	Screening not more than 24h before randomization	Day 1 (at-or up to 24h after random-ization)	Day 2	Day 4	Day 8	Day 15	Day 22	Day 28 (if still in hospital)	ICU discharge	Hospital discharge	Day 28	Day 60 (+/- 3 days) after randomization
Deferred informed consent[a]	X											
Screening / Baseline Assessments												
Inclusion/exclusion criteria	X											
Urine analysis	X											
Pregnancy test[b]	X											
Weight	X											
Height	X											
PaO_2 / FiO_2[c]	X											
Demographics, COVID-19 history, SARS-CoV-2 mRNA test[d]	X											
Medical history/ concomitant disease	X											
Prior medications and procedures	X											
Intubation date	X											
Randomization												
Randomization	X											
IMP Administration												
IMP administration[e]		**X**	**X**	**X**	**X**	**X**	**X**					

	Screening/ Randomization	Treatment Period IMP administration and assessments as long as in ICU / Hospital									Follow-up Period (Telephone possible)	
		Week 1			Week2	Week 3	Week 4	Week 5	Any time		FUV	
	Screening not more than 24h before randomization	Day 1 (at or up to 24h after random-ization)	Day 2	Day 4	Day 8	Day 15	Day 22	Day 28 (if still in hospital)	ICU discharge	Hospital discharge	Day 28 after randomization	Day 60 (+/- 3 days) after randomization
Endpoint Assessments												
Organ support (renal replacement therapy, ECMO, mechanical ventilation)		X										
Extubation and re-intubation date(s)		X										
Ordinal scale evaluation[f]	X				X	X	X	X	X	X	X	
Survival status		X									X	X
Quality of life (EQ-5D)												X
Glasgow Outcome Scale												X
Safety Assessments												
Safety laboratory tests[g]	X	X	X	X	X	X	X	X	X	X		
Creatinine[h]	X	X	X	X	X	X	X	X	X	X		
Vital signs[i]		X	X	X	X	X	X	X	X	X		
Adverse events[j]	X	X									X	X
Physical examination[l]	X	X	X	X	X	X	X					
Concomitant medications and procedures		X										
12-lead ECG	X								X			
PK/PD Assessments (Country-specific)[k]												
IFX-1 sample	X				X					X		

	Screening/ Randomization	Treatment Period IMP administration and assessments as long as in ICU / Hospital									Follow-up Period (Telephone possible)	
		Week 1			Week2	Week 3	Week 4	Week 5	Any time		FUV	
	Screening not more than 24h before randomization	Day 1 (at or up to 24h after random-ization)	Day 2	Day 4	Day 8	Day 15	Day 22	Day 28 (if still in hospital)	ICU discharge	Hospital discharge	Day 28 after randomization	Day 60 (+/- 3 days) after randomization
ADA sample	X									X		
C5a sample	X				X					X		

ADA = anti-drug antibody; C5a = complement factor 5a; COVID-19 = Coronavirus Disease-19; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; EQ-5D = EuroQol 5-D; FUV = follow-up visit; ICU = intensive care unit; IMP = investigational medicinal product; IV = intravenous; PaO_2 / FiO_2 = oxygenation index; PK/PD = pharmacokinetic/pharmacodynamic; SARS-CoV-2 = Severe acute respiratory syndrome Coronavirus 2.

a Obtaining of informed consent is proposed to be deferred or by any other legally acceptable local consent procedure for the ICU patients in this study (see Section 6.3).
b Serum or urine samples for pregnancy testing will be collected only for women of childbearing potential.
c PaO_2 / FiO_2 should be assessed within 6h before randomization (one representative measurement)
d SARS-CoV-2 infection confirmation will be done, if not already tested positive in last 14 days before randomization, with locally available test system
e Up to 6 treatments of IMP will be administered at days 1, 2, 4, 8, 15, and 22 as long as the patient is still in the hospital, even if discharged from the ICU.
f 8-point ordinal scale score will be documented at the visits indicated, including the date (one value per assessment day, that best represents the patient's condition at that day)
g Day 1 assessment has to be done prior to IMP administration only, if more than 12 h elapsed between screening assessment and IMP administration. Safety laboratory tests include hematology (hemoglobin, hematocrit, platelet count, red blood cell count, red blood cells (MCV), white blood cell count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils), coagulation parameters (activated partial thromboplastin time [aPTT], prothrombin time [PT], D-dimer), blood chemistry (ALT, AST, lactate dehydrogenase [LDH], total bilirubin, and c-reactive protein [CRP]) (see Appendix 1, Table 4). Blood samples for safety laboratory analysis should be obtained at indicated days during routine sampling (one representative value, if taken more than once a day).
h Creatinine assessment should be obtained at indicated days during routine sampling (one representative value, if taken more than once a day). Day 1 assessment has to be done prior to IMP administration only, if more than 12 h elapsed between screening assessment and IMP administration.
i Vital signs (core body temperature, heart rate, respiratory rate, blood pressure [diastolic and systolic]) will be assessed at indicated visits at pre-dose within 1h before administration of IMP (one representative measurement closest to IMP administration) and at further time points whenever medically indicated. Blood pressure and heart rate measurements will be assessed with an intra-arterial catheter, or a completely automated device. Manual techniques will be used only if an automated device is not available.
j Adverse event reporting will follow special considerations for the ICU setting as described in Section 9.1 ff and Appendix 3.
k PK/PD sampling will be conducted at selected countries/sites. PK/PD samples will be taken within 1h before administration of IMP.
l Day 1 assessment has to be done prior to IMP administration only, if more than 24 h elapsed between screening assessment and IMP administration.

3. INTRODUCTION AND BACKGROUND INFORMATION

3.1. Background

There are daily increasing numbers of Severe Acute Respiratory Syndrome (SARS) Coronavirus 2 (SARS-CoV-2) infected individuals globally and reports on impact / mortality vary constantly. As of 23 July 2020, over 15 million documented cases were reported worldwide of which more than 619,000 died (World Health Organization [WHO] 2020). Clinical manifestations of Coronavirus Disease-19 (COVID-19) vary, with approximately 5% of patients having critical manifestations (such as respiratory failure, septic shock, and/or multiple organ dysfunction) and 17-35% of hospitalized patients being treated in an intensive care unit (ICU), of whom 29-91% require invasive mechanical ventilation (Wiersinga et al. 2020).

The main COVID-19 characterizing clinical features are age greater than 50 years and presence of comorbidities such as hypertension and diabetes, whereas main laboratory findings show hepatic and renal dysfunction in the presence of leukopenia, lymphopenia, increase of D-dimers, and strong inflammatory cytokine activation (Guan et al. 2020; Huang et al. 2020; Liu et al. 2020; Garg et al. 2020; Wiersinga et al. 2020). Elevated D-dimer values have been shown to be strongly associated with poorer prognosis. It is also reported that the complement cascade is highly activated (Gao et al. 2020). One hallmark of progressed disease in patients who become severely diseased is the association of blood neutrophil increases with the disease severity, and neutrophil infiltration in the heart and liver.

Monoclonal antibodies directed against key inflammatory mediators, such as interleukin 1 and 6 and complement factor 5a (C5a), aim to modulate the overwhelming inflammatory response following SARS-CoV-2 infection, thereby preventing organ damage (Wiersinga et al. 2020). These targeted immunomodulatory agents are currently being evaluated for the management of COVID-19 and may prevent disease progression in hospitalized patients.

3.2. Study Rationale

3.2.1. Drug Profile

IFX-1 is a chimeric immunoglobulin G4 (IgG4) monoclonal anti-human C5a antibody, which specifically binds to the soluble human complement split product C5a. IFX-1 has been demonstrated to block C5a-mediated biological effects with high efficacy in vitro. C5a is one of the most potent inflammatory factors, triggering innate immune responses and bridging to adaptive immune responses (Dunkelberger and Song 2010). In blood, C5 is cleaved to C5a by components of the classical and alternative complement pathway, and the coagulation pathway, whereas in tissue, factors of the alternative complement and the coagulation pathway factors play a major role in C5a generation (Hess and Kemper 2016).

3.2.2. Non-clinical and Therapeutic Studies

Non-clinical studies were conducted to assess pharmacological and toxicological aspects of IFX-1 and showed that IFX-1 was able to rapidly bind to its target, the human C5a, and achieve an almost complete blockade of C5a-induced biological effects. At the same time, cleavage of C5 and formation of the complement membrane attack complex was not disrupted in vitro.

IFX-1 did not demonstrate any cross-reactivity or bioactivity in species other than humans and non-human primates (Section 4.2 of the Investigator Brochure [IB]). Therefore, toxicology studies were only conducted in cynomolgus monkeys.

IFX-1 has been investigated in viral-induced lung injury in monkeys infected with the avian flu virus H7N9. It had been shown that the neutrophil influx into the lung as well as the lung damage could be greatly reduced by this therapeutic attempt. In addition, the viral replication was greatly reduced as well, which is believed to be an indirect effect (Sun et al. 2015). This research was in line with findings generated in an H5N1 model of disease in rodents (Sun et al. 2013). Since then, the role of complement and specifically C5a for viral-induced lung injury has become an accepted concept in basic research (Wang et al. 2015). The same research group then confirmed the role of the C5a/C5a-receptor signaling axis for viral replication, for lung neutrophil influx and damage in a mouse model of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (Jiang et al. 2018). Another group of researchers then confirmed the role of complement activation and made similar findings on viral replication inhibition and lung damage reduction in complement deficient mice in a SARS virus infection model (Gralinski et al. 2018). One finding of this study was that complement deficient mice (C3-/-) had significantly less infiltration of the lungs with neutrophils and monocytes, also confirming earlier findings in greater detail for SARS-CoV induced viral lung injury.

This body of research has led to the approval by the Chinese FDA of two ongoing trials in SARS-CoV-2 infected patients in China with the monoclonal anti-C5a antibody BDB-1 (S-FDA approval number 2020L00003). BDB-1 is generated from the InflaRx IFX-1 cell line which has been transferred and licensed to the InflaRx collaborator Beijing Deferengui Biotech Co. (BDB). BDB develops BDB-1 under their responsibility in China and InflaRx has all rights to any discoveries made by BDB-1 globally outside China, where InflaRx develops IFX-1 in the rest of the world. The BDB-1 trials are ongoing, however data of the first two open label treated patients were reported in context of a research article by Gao et al. 2020 (see Section 3.2.4).

None of the Good Laboratory Practice-compliant studies in cynomolgus monkeys revealed relevant toxicological or safety concerns for IFX-1. During single-dose and repeat-dose administration of IFX-1 at doses of up to 50 mg/kg body weight in cynomolgus monkeys no direct IFX-1-related toxicological or adverse findings within an extended core battery of safety pharmacology assessments were observed. Results showed dose-related increases in systemic and maximum exposure in the investigated dose range of 1 to 50 mg/kg body weight. Anti-drug

antibodies (ADAs) were detected in 1 animal in the 26-week repeat-dose study. This animal died, most likely because of an ADA-mediated immune complex formation.

An overview of the non-clinical toxicology studies that were conducted with IFX-1 is available in Table 8 of the IB.

For further details, refer to Section 4 of the IB.

3.2.3. Experience in Humans

At the time of writing of Protocol Version 2.0, Phase II of the current study has been completed and all 30 enrolled patients have been treated (15 in Arm A [best supportive care (BSC) + IFX-1] and 15 in Arm B [BSC alone]) for up to 28 days. Relative change (%) from baseline to day 5 in oxygenation index was assessed as the primary endpoint along with additional clinical parameters until day 28. Relative change in the oxygenation index at day 5 showed no differences between treatment groups. However, IFX-1 treatment was associated with a lower 28-day all-cause mortality when compared to the BSC arm, along with trends in disease improvement, as evidenced by fewer patients experiencing renal impairment assessed by eGFR, more patients showing reversal of blood lymphocytopenia and a greater lowering of lactate dehydrogenase concentrations. In IFX-1-treated patients, pulmonary embolisms (PE) reported as serious adverse events (SAEs) were lower compared to the BSC arm. Also, a temporary increase of D-dimer levels, as potential expression of induction of blood clot lysis, was detected in the first days after initiation of IFX-1 treatment.

Over a treatment period of 28 days, patients in the IFX-1 arm received a maximum of 7 doses of 800 mg IFX-1 intravenously (IV) on separate days. At randomization, 18 patients (60%) were intubated, and 12 patients (40%) had other oxygen supply. A higher number of patients with 2 or more comorbidities associated with increased COVID-19 mortality were reported in the IFX-1 treatment arm compared to the BSC arm. Twenty-eight-day all-cause mortality in the IFX-1 treatment arm was 13% (2 out of 15) versus 27% (4 out of 15) in the BSC arm. In the BSC arm, 4 patients died of COVID-19-induced multi-organ failure, and 3 of them had PE reported as SAEs. In the IFX-1 arm, one patient died after an acute ventilator tube complication (leakage) and one patient with a history of severe chronic obstructive pulmonary disease died of pulmonary failure. Serious AE rates were comparable between groups, but the rate of PE reported as SAEs was substantially lower in the IFX-1 treatment group. Upon review of the safety data, the independent data safety monitoring board has recommended continuation of the trial into Phase III.

IFX-1 is also being developed for the treatment of other inflammatory diseases. Five clinical studies in humans have been completed so far. One Phase I study in healthy volunteers (Study IFX-1-P1.1) and 4 Phase II studies: 1 in patients with early septic organ dysfunction (Study IFX-1-P2.1), 1 in patients undergoing complex cardiac surgery (Study IFX-1-P2.2), and 2 in patients with hidradenitis suppurativa (HS) (Studies IFX-1-P2.3 and IFX-1-P2.4; Section 5 of the IB).

To date, 391 subjects (26 healthy volunteers and 365 patients) have been treated in completed clinical studies of these other inflammatory diseases, of which 294 have received IFX-1 and 92 have received placebo. IFX-1 was safe and well tolerated, with no dose relationship in the safety findings. No specific adverse reactions emerged in clinical studies of single or multiple doses IFX-1 in healthy volunteers or patients with cardiac disease, sepsis, or HS.

Currently, 4 further Phase II studies are ongoing: 1 in patients with HS (Study IFX-1-P2.4; in final analyses), 2 in patients with granulomatosis with polyangiitis and microscopic polyangiitis (also referred to as anti-neutrophil cytoplasmic antibody-associated vasculitis; Study IFX-1-P2.5 and IFX-1-P2.6), and 1 in patients with pyoderma gangrenosum (Study IFX-1-P2.7).

Data are available from the interim analysis of the main period of the Phase II Study IFX-1-P2.4 in HS, where 141 patients were treated with IFX-1 in 4 different IFX-1 dose cohorts (400 mg and 800 mg every 4 weeks, 800 mg bi-weekly, and 1200 mg every 2 weeks) and 36 patients were treated with placebo. The total treatment duration in this study, which recently completed treatment, was 9 months. Treatment with IFX-1 was safe and well tolerated with rare occurrence of AESIs, defined as infusion reactions, including hypersensitivity or anaphylaxis, meningitis, meningococcal sepsis, and invasive infection. Four patients experienced AEs suggestive of hypersensitivity. The reactions were moderate, and treatment continued, if necessary with adequate prophylactic medication. Anti-drug antibodies during treatment were observed in a range of 5.6% to 12.9% with a trend towards increasing frequency with low dose and larger administration intervals.

3.2.4. Scientific Rationale for the Study

Neutrophil driven tissue and organ damage is known to play an important role in a wide array of acute inflammatory diseases. The mechanism leading to damage has been largely attributed to two mechanisms: 1) the release of granular enzymes and 2) the generation of so-called reactive oxygen species in which O_2 radical formation elicits a damaging effect.

One of the strongest chemoattractant substances, which is also capable of inducing both mechanisms described above is the human complement split product C5a.

Earlier research by InflaRx has demonstrated that the anti-human C5a antibody IFX-1 could significantly reduce the neutrophil and macrophage infiltration in a model of viral (H7N9)-induced lung injury in monkeys (Sun et al. 2015). This was accompanied by a significantly reduced tissue damage in the lung of infected animals and also a significantly reduced viral replication when compared to mock-treated animals. The mechanism was then confirmed in a model of MERS–CoV-induced lung injury where similar findings were made by using an anti-C5a receptor antibody (Jiang et al. 2018) and in a model of SARS-CoV-induced lung injury by using complement C3 knockout mice (Gralinski et al. 2018). The latter study also provided evidence for a profound complement activation in SARS virus infections in animals. These studies all suggested a role of neutrophil driven lung damage, which was induced by generation of C5a in different viral-lung injury models, including SARS viruses.

Latest data from a collaborating research group in China demonstrated strongly and significantly elevated C5a levels in severely diseased COVID-19 patients when compared to mildly diseased patients (Gao et al. 2020; Carvelli et al. 2020) and revealed evidence for a strong complement pathway driven activation of C5a in this disease. In addition, data from the first two severely diseased COVID-19 patients treated with the IFX-1 cell line derived anti-C5a antibody BDB-1, which InflaRx licensed to a collaborator in China, demonstrated clinical improvement in oxygenation index, fever reduction, and laboratory parameter normalization including liver enzymes and lymphocyte counts.

From a clinical perspective, various papers have confirmed that COVID-19 infected non-surviving patients demonstrated lung failure with close to 100% (Zhou et al. 2020) and that, in contrast to surviving patients, non-survivors demonstrated elevated white blood cell counts and neutrophils above the normal range (Wang et al. 2020; Gong et al. 2020).

In summary, there is evidence that in COVID-19 patients who are severely affected, C5a activation occurs to a large extent and that neutrophil count elevation in blood is associated with bad outcome. These human data fit well to the scientific rationale developed in animal models of viral-induced lung injury that activated neutrophils attracted to the lung may cause viral-induced lung damage. First treatment attempts with the anti-C5a antibody technology developed by InflaRx (BDB-1) in severely affected COVID-19 patients provide further evidence for the scientific rationale.

The completed Phase II portion of the current trial was exploratory in nature and was not powered to show statistically significant differences in clinical endpoints. Relative change (%) from baseline to day 5 in the oxygenation index, chosen as the primary endpoint for Phase II, showed a large variability and dependency on patient positioning and intubation status which excluded this endpoint from being used in a confirmatory study. Phase III of the study is an adequately powered, placebo-controlled, double blinded phase evaluating standard of care (SOC) + IFX-1 versus SOC + placebo-to-match with 28-day all-cause mortality as the primary endpoint, an accepted regulatory primary endpoint for critical care studies.

At the time that Phase II of this study was initiated, there was no SOC established for this newly identified disease. The SOC to be utilized in Phase III of this study reflects the current understanding of the SOC for hospitalized patients with COVID-19, which includes venous thromboembolism (VTE) prophylaxis at a minimum, and may include other international and country-specific recommended treatments for COVID-19 per the locally adopted treatment recommendations.

3.2.5. Justification for Dose

The aim for determining the dose and administration frequency for IFX-1 is to establish a pragmatic administration schedule for the COVID-19 patient population. IFX-1 dose and administration schedule was chosen based on prior pharmacokinetic (PK)/pharmacodynamic (PD) observations for IFX-1 trough values and blood C5a levels, dose-response assessment in

Study IFX-1 P2.4 in HS, and the described unprecedented high C5a levels in patients with severe COVID-19 related pneumonia (Gao et al. 2020; Carvelli et al. 2020). In a population PK/PD modelling study for IFX-1 based on the data of the 2 trials in HS patients, a reduction in C5a concentration was found to be dependent on all measures of drug exposure, with increasing exposure predicting a greater reduction in C5a.

The observed half-life of IFX-1 with a single dose of 800 mg was 3 to 4 days in Study IFX-1 P2.2 in patients undergoing complex cardiac surgery. Thus, an additional dose of 800 mg at Day 4, followed by weekly administration of 800 mg IFX-1 was chosen for Study IFX-1 P2.3 in patients with HS.

In Study IFX-1 P2.3 in patients with HS, 800 mg once-weekly IFX-1 was administered for up to 9 times including an additional dose of 800 mg at Day 4. This administration schedule resulted in IFX-1 trough concentrations of around 50 µg/mL and a decrease of elevated baseline C5a levels to approximately detection limit throughout the treatment duration in the majority of patients. This dosing regimen was well tolerated, with no new safety signals, and clinical improvement of HS was observed in some patients.

In another clinical study in HS (Study IFX-1 P2.4), 4 different dosing schedules were explored, of which the highest dose was 1200 mg every 2 weeks. Safety findings were similar in all dose groups, and similar to safety findings in previous studies, with no new specific AESIs.

Based on the above data, the dosing schedule of IFX-1 for this study includes an additional dose of 800 mg IFX-1 at day 2 in the established fractionated loading dose scheme, that foresees administration of 800 mg at days 1, 4, and 8. This additional dose has been chosen due to the reported high C5a levels in COVID-19 patients (Gao et al. 2020). Therefore, the entire dosing scheme contains up to 6 IFX-1 doses of 800 mg at days 1, 2, 4, 8, 15, and 22 (or less until hospital discharge). This regimen had been employed in Phase II of this study, leading to a lower death rate and supporting efficacy signals without any new signals of unknown toxicities (Vlaar et al 2020).

3.3. Benefit/Risk Assessment

IFX-1 is a chimeric IgG4 antibody that has the potential to elicit infusion reactions, including hypersensitivity or anaphylaxis. In animal studies, one unexplained death of a cynomolgus monkey retrospectively showed development of anti-IFX-1 antibodies. In clinical studies, few patients tested positive for anti-IFX-1 antibodies, and only mild to moderate signs of hypersensitivity reactions were occasionally observed so far (overall ADA rate in the range of 5% to 13%). In total, IFX-1 showed very good tolerability in clinical studies. The majority of observed AEs were attributed to the underlying diseases and IFX-1 AESIs occurred occasionally (see IB for details).

A summarized in Section 3.2.4, there is evidence that in COVID-19 patients who are severely affected, C5a activation occurs to a large extent and that neutrophil count elevation in blood is associated with worse outcomes.

Data from the interim analysis from the completed Phase II of the current study demonstrated that IFX-1 treatment was associated with a lower 28-day all-cause mortality when compared to the BSC arm, along with trends in disease improvement, as evidenced by fewer patients experiencing renal impairment, more patients showing reversal of blood lymphocytopenia, and a greater lowering of lactate dehydrogenase concentrations. In IFX-1-treated patients, PE reported as SAEs were lower compared to the BSC arm. Also, a temporary increase of D-dimer levels, as potential expression of induction of blood clot lysis, was detected in the first days after initiation of IFX-1 treatment.

Overall, the expected clinical benefit for patients suffering from COVID-19-related severe pneumonia outweighs the risks in relation to the mild to moderate side effects that have been attributed to IFX-1 so far.

4. OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objectives

The primary objective of Phase II was:

- To explore the effect of IFX-1 on COVID-19 related severe pneumonia (hypothesis generating)

The primary objective of Phase III is:

- To demonstrate the efficacy of IFX-1 to improve survival outcomes of severe COVID-19 pneumonia (confirmative)

4.1.2. Secondary Objectives

The secondary objectives of Phase II and Phase III are:

- To assess and define other parameters of efficacy
- To assess the safety of IFX-1

4.2. Study Endpoints

4.2.1. Phase II

4.2.1.1. Primary Endpoint

The primary endpoint in Phase II was the relative change (%) from baseline (day 1 prior to study drug administration at ± 1h of randomization) in oxygenation index (PaO_2 / FiO_2) in supine position at day 5.

4.2.1.2. Secondary Endpoints

The secondary endpoints in Phase II were:

- Number of patients (%) achieving an **Early Response** as defined as meeting ALL of the following criteria at day 7 after enrollment:
  - Patient alive and extubated OR oxygenation index ≥ 300 OR improvement of ≥ 30% from baseline
  - Temperature < 38°C in absence of fever decreasing medication of at least 4h
  - White blood cell count within normal limit of local lab quantifications
- Number of patients (%) reaching a **Late Response** as defined by either being **discharged alive** from hospital until day 28 **OR** meeting **ALL** of the following criteria at day 28 of the trial
  - Patient alive and extubated
  - Patient discharged from ICU
  - Patient free of shortness of breath (respiratory rate < 20) in absence of oxygen supply
  - Patient free of fever (< 37.6°C)
- Relative change (%) from baseline (day 1 prior to study drug administration at ± 1h of randomization) in oxygenation index (PaO_2 / FiO_2) in supine position at day 3, 7, 9, and 11.
- All cause 28-day mortality (%)
- Frequency, severity, and relatedness to study drug of treatment-emergent adverse events (TEAEs) and SAEs

4.2.1.3. Other Endpoints

The other endpoints in Phase II were:

- Change from baseline in alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
- Change from baseline in troponin I adjusted to glomerular filtration rate
- Change from baseline in creatinine

- Change from baseline in lymphocyte counts
- Change from baseline in neutrophil counts
- Change from baseline in D-dimers
- Change from baseline in Glasgow Outcome Scale
- Time to reach ICU discharge criteria as defined by ALL of the three criteria below:
  - Alive and extubated
  - No need for continued (>3h per day) non-invasive ventilation
  - Free of vasopressor and inotropic therapy
- Assessment of complement activation parameters and plasma concentrations of IFX-1

4.2.2. Phase III

4.2.2.1. Primary Endpoint

Based on the preliminary interim analysis of efficacy data from Phase II, the primary endpoint chosen for Phase III is 28-day all-cause mortality.

4.2.2.2. Secondary Endpoints

The secondary endpoints in Phase III are:

- 60-day all-cause mortality (proportion of patients deceased until Day 60)
- Proportion of patients with an improvement in the 8-point ordinal scale (Appendix 7) (day 15, day 28)
- Proportion of patients developing acute kidney failure (eGFR < 15 mL/min/1.73m², assessed by the CKD-EPI equation requiring race information) during ICU stay and at day 28
- Proportion of patients free of any renal replacement therapy within 28 days upon randomization
- Frequency, severity, and relatedness to study drug of serious and non-serious TEAEs

4.2.2.3. Other Endpoints

The other endpoints in Phase III are:

- Time to first extubation
- Proportion of patients achieving 8-point ordinal scale score 3 or below (patients alive and free of respiratory failure) at day 15 and day 28
- Glasgow Outcome Scale score assessed at study day 60
- Quality of life assessed by EuroQol 5-D (EQ-5D) at study day 60.

5. STUDY DESIGN

5.1. Overall Design

This is a pragmatic, adaptive, randomized, multicenter phase II/III study evaluating IFX-1 for the treatment of COVID-19 related severe pneumonia. The study consists of two parts: Phase II, an open-label, randomized, 2-arm phase evaluating BSC + IFX-1 (Arm A) and BSC alone (Arm B); and Phase III, a double-blind, placebo-controlled, randomized phase evaluating SOC + IFX-1 (Arm A) and SOC + placebo-to-match (Arm B). The SOC includes VTE prophylaxis at a minimum, and may include other international and country-specific recommended treatments for COVID-19 per the locally adopted treatment recommendations. An independent safety monitoring board in phase II part and an independent data monitoring board (IDMC) in phase III part are established to monitor the patients' safety in an ongoing manner (see Sections 5.3 and 5.5).

At the time of writing of Protocol Version 2.0, Phase II of the study has been completed and all 30 patients have been treated (15 in Arm A [BSC + IFX-1] and 15 in Arm B [BSC alone]). A preliminary interim analysis has been performed to assess the clinical benefit of the treatment using the assessed clinical parameters. An expert committee (EC) has monitored safety and the supported re-definition of clinical endpoint(s) for Phase III.

In Phase II, patients in Arm A were treated with a maximum of 7 IV doses of IFX-1 800 mg over a period of 29 days. The first 5 treatments at days 1, 2, 4, 8, and 15 were administered to all patients randomized into Arm A. Treatment at day 22 was only administered in the event that a patient has not been extubated and discharged from ICU. In case a patient's clinical situation worsened after day 8, although an initial clinical benefit was observed, one additional administration of 800 mg IFX-1 between day 11 and 13 could have been given at investigator discretion. Loss of clinical benefit could in this situation relate to the exceptionally high C5a levels observed in some cases of COVID-19 related pneumonia and associated shortened IFX-1 half-life.

Phase III of the study will randomize up to 400 patients with one interim analysis for stopping for futility. A total of 180 patients are planned to be randomized into Arm A and Arm B using a 1:1 allocation ratio for the first stage; based on results of the interim analysis, up to an additional 180 patients are planned to be randomized using the same allocation ratio for the second stage. Additional patients will be randomized under the following conditions:

- For patients who were erroneously randomized (screening failures) and did not get IMP treatment.
- For patients who were randomized but consent was withdrawn (either by the patient or patient representative) within the first 48 hours after randomization, irrespective of whether IMP was administered or not.

The primary statistical analysis will be based on all randomized patients except patients randomized in error (reason for early termination documented as "Randomized by mistake" in the eCRF) who did not get IMP treatment.

In Phase III, patients will be treated with a maximum of 6 IV doses of IFX-1 800 mg (Arm A) or placebo (Arm B) at days 1, 2, 4, 8, 15, and 22, as long as the patient is still in the hospital (even if discharged from the ICU).

Patients will be assessed for quality of life using the EQ-5D.

Patients will be followed for survival and their clinical status assessed by the Glasgow Outcome Scale.

5.1.1. Method of Treatment Assignment

In Phase II, patients were centrally assigned to a treatment arm by the Investigator via the randomization module of the electronic case report form (eCRF). The investigational medicinal product (IMP) was assigned to each patient by the investigator at the investigation site. Sites were each given a randomization block and instructed to assign the first patient to Arm A, the second patient to Arm B, etc. The site recorded the IMP assignment on the applicable eCRF, if required.

In Phase III, patients will be centrally assigned to a treatment arm by the investigator via an Interactive Web Response System (IWRS). IMP will be assigned to each patient by the IWRS.

IMP shipment to sites will be automatically triggered by the IWRS, and will be initiated, maintained, and controlled by the IWRS.

IMP is dispensed at the study visits as summarized in the schedule of assessments (SoA, Table 1 and Table 2).

5.1.2. Blinding

Phase II of the study was open-label and randomized, while Phase III will be double-blind, placebo-controlled, and randomized.

Phase III: Emergency Identification of Investigational Medicinal Product

Breaking of the treatment-assigned blind will be performed in the IWRS (please refer to the Interactive Response Technology Study User Guide for instructions on unblinding). Any premature breaking of the blind should be confined to emergency cases in which knowledge of the IMP received is necessary, e.g., to be able to provide appropriate emergency medical treatment. Before breaking the blind, the investigator should contact the medical monitor whenever possible, unless this would delay the emergency treatment. Subject safety must always be the primary consideration when determining whether to break the blind.

Investigators will be provided with the appropriate IWRS access to unblind the treatment assignment of an individual subject.

If a subject's treatment assignment is unblinded, the required personnel will receive an alert from the IWRS. In addition, the investigator must inform the medical monitor within 24 hours of breaking the blind and the subject will be discontinued from further IMP treatment. The date and reason why the blind was broken must be provided by the investigator and recorded in the source documentation and in the eCRF, as applicable.

5.2. Patient Enrollment

In Phase II, patients were randomized to Group A or B. The maximum number of randomized patients in Phase II was set to 30. There was a recruitment stop after the planned number of patients for Phase II were enrolled. After the preliminary interim analysis of Phase II was performed and the EC recommended to proceed, the number of patients for Phase III was calculated according to the established hypothesis. For details on the role of the EC, see Section 5.4.

In Phase III, 180 patients are planned to be randomized into Arm A and Arm B using a 1:1 allocation ratio for the first stage; based on results of the interim analysis, up to an additional 180 patients are planned to be randomized using the same allocation ratio for the second stage.

For patients randomized in error (screening failures) and patients for whom consent is withdrawn within 48 hours after randomization, additional patients will be randomized. Depending on the number of patients meeting criteria for additional randomization, more than 360 patients will be randomized but not more than 400.

5.3. Independent Safety Monitoring Board for Phase II

An independent Safety Monitoring Board (iSMB) was constituted to support safety surveillance in both treatment arms throughout Phase II and Phase III of the study. The committee included at least 2 Intensive Care specialists not involved as investigators in this study and an independent statistician.

The iSMB monitored the safety of all patients regularly, after 10, 20, and 30 patients completed their treatment in Phase II. At each review, the iSMB recommended on continuing or ending the study. After completion of Phase II (30 patients), the iSMB has assessed the totality of available data of all patients and has recommend on proceeding to Phase III (see Section 3.2.3).

5.4. Expert Committee for Phase II

An EC was constituted to support efficacy surveillance in both treatment arms throughout Phase II of the study. The committee included the clinical study monitor and at least 3 Intensive

Care specialists involved in the treatment of COVID-19 affected patients (Coordinating Investigator included).

The committee monitored the efficacy of all patients regularly, after 10, 20, and 30 patients completed their treatment. At each review, the EC was able to recommend on continuing or ending the study.

After completion of Phase II (30 patients), the EC assessed the totality of the data of all patients, taking into account the recommendations of the iSMB and recommend proceeding to Phase III, assessed appropriateness of the endpoints and scheduled assessments, and supported establishing an adequate hypothesis for Phase III.

The EC has stopped meeting at the beginning of Phase III (i.e., at the time of writing of Protocol Version 2.0).

5.5. Independent Data Monitoring Committee for Phase III

In Phase III, the iSMB from Phase II will continue as an Independent (Clinical Trial) Data Monitoring Committee (IDMC). The IDMC will meet every 3 months throughout Phase III of the study to further assess safety. In addition, the IDMC will perform an unblinded assessment of the data of the interim analysis and will make recommendations on whether to continue the study or not according to the predefined early stop criterion (see Section 10.2.3.5). All available data will be provided to the IDMC before each meeting. Details will be described in a separate IDMC Charter.

5.6. Patient and Study Completion

5.6.1. Phase II

5.6.1.1. End of Treatment and Follow-up

End of treatment (EOT) was defined as last planned administration or discontinuation of IMP for other reasons. The EOT telephone visit (Follow-up Visit [FUV] 1) was to occur 28 days after last study drug administration in Phase II. The visit information obtained via the telephone call (e.g., AEs, survival status) was to be recorded.

Discontinuation of study treatment did not represent withdrawal from the study.

For details on treatment discontinuation criteria, see Section 7.2.4.

5.6.1.2. End of Study

Patients were to be followed for survival using the Glasgow Outcome Scale until the end of study (EOS) visit (FUV 2). If required, information could have been obtained by a telephone call.

The EOS for the individual patient was defined as the date of the last contact of the 2-month follow-up period, date of death, date of consent withdrawal from study participation (see Section 5.6.1.3), or the date of last contact when patients were lost to follow-up (see Section 5.6.1.4).

The entire study was to end when all patients discontinued IFX-1 AND all patients ended the study as described above.

The sponsor could have prematurely terminated Phase II of the study at any time earlier than planned for the following reasons:

- Unacceptable toxicity
- Administrative reasons

5.6.1.3. Consent Withdrawal/ Discontinuation of Study Participation

A patient could have withdrawn from Phase II of the study at any time at his/her own request without the need to provide any reason(s).

If the patient withdrew from study participation, the sponsor could have retained and continued to use any data collected before such a withdrawal of consent. However, in the case of deferred informed consent, if the consent was not obtained or if a legal representative denied the patient's participation in the study, the patient was excluded and data were no longer to be used (see Section 6.3). Patients (or legal representatives) who wished to withdraw consent/discontinue the study while still on treatment should have been encouraged by the investigator to perform the EOT visit for their own safety before any further data collection for study purposes was terminated.

If a patient withdrew from the study, he/she could have requested destruction of any samples taken and not tested, and the investigator must have documented this in the site study records.

5.6.1.4. Lost to Follow-up

A patient was to be considered lost to follow-up if he or she could not be reached after hospital discharge for scheduled contacts and the study site was unable to make contact as described below.

The following actions must have been taken if a patient could not be reached:

- The site must have attempted to re-contact the patient as soon as possible after the failed first scheduled contact.
- Before a patient was deemed lost to follow-up, the investigator or designee must have made every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts were to be documented in the patient's medical record.

- Should the patient have continued to be unreachable, he/she was considered to have been withdrawn from the study with a primary reason of lost to follow-up.

5.6.2. Phase III

5.6.2.1. End of Treatment and Follow-up

End of treatment (EOT) is defined as the last planned administration or discontinuation of IMP for other reasons.

The FUV is scheduled to occur 28 days (if patient has been discharged) and 60 days after the randomization date. The visit information obtained at a site visit or via telephone call (e.g., AEs, survival status, according to the SoA, Table 2) should be recorded.

Discontinuation of study treatment does not represent withdrawal from the study.

For details on treatment discontinuation criteria, see Section 7.2.4.

5.6.2.2. End of Study

The end of study for the individual patient is defined as the date of the last contact of the follow-up period (i.e., 60 days after randomization), date of death, date of consent withdrawal from study participation (see Section 5.6.2.3), or the date of last contact when patients are lost to follow-up (see Section 5.6.2.4), whatever occurs earliest.

The entire study will end when all patients have discontinued IFX-1 AND all patients ended the study as described above.

The sponsor may prematurely terminate the study at any time earlier than planned for the following reasons:

- Unacceptable toxicity
- Administrative reasons

5.6.2.3. Consent Withdrawal/Discontinuation of Study Participation

A patient may withdraw from the entire study at any time at his/her own request without the need to provide any reason(s).

If the patient withdraws /patient is withdrawn by legal representatives/relatives from study participation, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. However, in the case of deferred informed consent, if the consent is not obtained or if a legal representative denies the patient's participation in the study, the patient is excluded and data will no longer be used, except if local regulations would permit the use of such data in this situation (see Section 6.3). Patients (or legal representatives/relatives) who wish to withdraw consent/discontinue the study while still on treatment should be encouraged by the

investigator to perform the FUV for their own safety before any further data collection will be stopped.

If a patient (or legal representatives/relatives) withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

5.6.2.4. Lost to Follow-up

A patient will be considered lost to follow-up if he or she cannot be reached after hospital discharge for scheduled contacts and the study site is unable to make contact as described below.

The following actions must be taken if a patient cannot be reached:

- The site must attempt to re-contact the patient as soon as possible after the failed first scheduled contact.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Study patients are considered enrolled into the study using a deferred consent procedure or another legally acceptable local consent procedure in this special ICU situation.

6.1. Phase II

6.1.1. Inclusion Criteria

Patients must have met all the following criteria at screening and at enrollment to be randomized into Phase II of the study:

1. At least 18 years of age or older
2. Clinically evident or otherwise confirmed severe pneumonia as evidenced by at least one of the following criteria:
3. Chest X-ray or computed tomography (CT) scan or magnetic resonance imaging (MRI) with pulmonary infiltrates consistent with pneumonia
4. Clinical history in past 14 days of newly developed severe shortness of breath (> 29 breaths / minute) in the absence of oxygen supply or spontaneous peripheral oxygenation ≤ 92 with

need for oxygen supply, or need for non-invasive or invasive ventilation (in conjunction with a positive test for SARS-CoV-2 infection)

5. Oxygenation index at time of enrollment (PaO_2 / FiO_2) ≤ 250 and ≥ 100 in supine position
6. SARS-CoV-2 infection confirmation (tested positive in last 14 days or test results to be obtained within 24h after enrollment, both with locally available test system).
7. No use OR stop of any corticosteroid treatment at time point of enrollment (topical treatment and systemic dose of ≤ 10mg prednisone / day equivalent allowed)

6.1.2. Exclusion Criteria

Patients who fulfilled any of the following criteria at screening were not eligible to participate in Phase II of the study:

1. Oxygenation index at time of enrollment (PaO_2 / FiO_2) < 100 or > 250 in supine position
2. Intubated > 48h at time point of enrollment
3. Patients who demonstrate an improvement in past 24h prior to enrollment in oxygenation and ventilation / support parameters which indicate an expected resolution of lung dysfunction in the next 24h without additional intervention according to judgment of the investigator with one or more of the following parameters present:
4. Improvement in oxygenation index of > 30% relative to previous measure (last 24h in supine position)
5. Extubation if intubated before
6. Known history of chronic obstructive pulmonary disease (COPD) (GOLD category C or D)
7. Known history of chronic dialysis OR received renal replacement therapy in past 14 days
8. Received new other biologic treatment attempt for COVID-19 in the past 14 days
9. Received treatment with a viral replication inhibitor in past 3 days
10. Known hypersensitivity to IFX-1 or any other ingredient of the study medication
11. Known pregnancy
12. Received organ or bone marrow transplantation in past 3 months
13. Known mechanically resuscitation in past 14 days
14. Patient moribund or expected to die in next 12h according to the judgment of the investigator
15. Patients otherwise considered restricted from receiving full supportive care (including ICU support)
16. Existing diagnosis of progressed cancer or other life-limiting disease with life expectancy < 6 months
17. Known to have received anti-cancer therapy for oncological disease in past 4 weeks

18. Known severe congestive heart failure (New York Heart Association [NYHA] Class III-IV; see Appendix 8)

6.2. Phase III

6.2.1. Inclusion Criteria

Patients must meet all the following criteria at randomization to be enrolled into Phase III of the study:

1. At least 18 years of age or older
2. Patient on invasive mechanical ventilation (but not more than 48h post intubation at time point of first IMP administration)
3. Patients with a PaO_2 / FiO_2 ratio of < 200 and > 60 at randomization (one representative measurement within 6h before randomization)
4. SARS-CoV-2 infection confirmation (tested positive in last 14 days before randomization with locally available test system)

6.2.2. Exclusion Criteria

Patients who fulfill any of the following criteria at randomization are not eligible to participate in Phase III of the study:

1. Intubated > 48 h at time point of first IMP administration
2. Expected stop of invasive ventilation or expected extubation in the next 24h without additional intervention according to judgment of the investigator
3. Known history of chronic dialysis OR received renal replacement therapy in past 14 days OR anticipated to receive renal replacement therapy within 24h after randomization
4. Known history of progressed COPD as evidenced by use of daily maintenance treatment with long-acting bronchodilators or inhaled/oral corticosteroids for > 2 months
5. Treatment of COVID-19 with investigational antibody treatment(s) which are not approved or not included in locally adopted treatment guidelines (e.g., WHO guidance, National Institutes of Health [NIH] COVID-19 treatment guidelines) for this indication in the past 7 days (Note: Antibody treatment[s] given within past 7 days for pre-existing diseases, other than COVID-19, are allowed.)
6. At time point of randomization, treatment of COVID-19 with investigational treatments which are not approved or not included in locally adopted treatment guidelines for this indication (e.g., WHO guidance, NIH COVID-19 treatment guidelines), including SARS-CoV-2 multiplication inhibitor(s) or immunomodulator(s). (Note: If a locally adopted treatment guideline recommends drugs such as remdesivir, dexamethasone, or anticoagulation, this would be allowed. Adopted guidelines and updates must be documented at study initiation and throughout the conduct of the study.)
7. Received cytokine adsorption therapy in past 3 days

8. Known hypersensitivity to IFX-1 or any other ingredient of the study medication
9. Serum or urine pregnancy test positive before randomization (required for women of childbearing potential)
10. Received organ or bone marrow transplantation in past 3 months
11. Known cardio-pulmonary mechanical resuscitation in past 14 days
12. Patient moribund or expected to die in next 24h according to the judgment of the investigator
13. Known to have received anti-cancer therapy for hemato-oncological disease in past 4 weeks OR known to have active malignant disease at time point of randomization
14. Known severe congestive heart failure (corresponding to e.g. NYHA Class III-IV, left ventricular ejection fraction <40%; see Appendix 8)
15. Known history of chronic liver disease (Child-Pugh B or C; see Appendix 11)
16. Participating in or has participated in other investigational interventional studies (drug or device) within the last 7 days before randomization

6.3. Deferred Consent and Other Forms of Informed Consent

In the Netherlands and Germany, we ask for deferred consent for patients in need of intensive care and we appeal to the emergency procedure for consent in medical research as stated in Article 6, Paragraph 4 of the Medical Research Involving Human Subjects Act (WMO, the Netherlands), §41 (1) of the Medicines Act (AMG, Germany), and other applicable country specific regulations, because of the following reasons:

It is very likely that the severity of the disease (severe pneumonia/acute respiratory distress syndrome) will result in a large proportion of patients unable to provide informed consent before the beginning of the trial either in oral or written form, mainly due to being on a ventilator or treated with drugs with sedative effects. COVID-19 related pneumonia resulting in the need for intensive care is a fast progressing disease. It requires immediate adequate treatment that cannot be postponed. So far, no treatment has been shown to address the underlying neutrophilic, inflammatory lung damage. Since IFX-1 blocks C5a, it has the potential to block neutrophil attraction to the lung. Moreover, it has been shown that COVID-19-related severe pneumonia is linked to extremely high C5a blood levels and related to a worse outcome of patients (Gao et al. 2020). In an ongoing study testing the biosimilar C5a antibody BDB-1, the first 2 patients treated showed a good recovery after being treated. Taken together, there is a possibility that treatment with IFX-1 will provide benefit specifically for patients with COVID-19-related severe pneumonia that require intensive care.

These severely ill patients are incompetent to give informed consent, and obtaining informed consent from a legal representative/relative may be almost impossible due to the current COVID-19-caused quarantine measures. Time to get informed consent from legal representatives/relatives will take at least half day, even by an experienced research team.

Patients have to be randomized at the ICU after inclusion and exclusion criteria have been checked and patients have been found to be eligible.

In the Netherlands, if the patient is incompetent to provide informed consent and a legal representative/relative cannot be reached in time, the investigator examines the patient, confirms and documents the patient's inability to provide consent as well as the urgency of participating in the trial with possible benefit to the patient. Informed consent from the patients, their relatives or their legal representative will be requested at the earliest appropriate time thereafter as applicable in the participating country. At minimum, the attempt of contacting the patient's relatives and the result of the contact will be documented in the patient's file.

In Germany, the investigator examines the patient and, if the patient is not able to consent, confirms and documents together with a consulting physician the patient's inability to provide consent as well as the urgency of participating in the trial with possible benefit to the patient. Informed consent from the patient will be requested at the earliest appropriate time thereafter. A further option in Germany may be the signing of the informed consent by the patients' legal representative.

In other participating countries where a deferred consent procedure is not legally acceptable, specific requirements will be laid out that will describe the country-specific legally acceptable procedure for retrieving consent from patients who are incompetent to provide consent or their relatives or their legal representatives, whatever will be applicable.

The hypothesis is that this group of intensive care patients can potentially benefit from participating in this study. While patients are exposed to the possible side effects of IFX-1, they will also receive SOC in Phase III.

6.4. Screening Failures

Screening failures are defined as patients who do not meet the criteria for participation in this study and thus, are either not randomized/assigned to IMP or randomized in error and do/did not receive IMP. Screen failure data for not randomized patients will not be recorded in the eCRF, for those patients who are randomized in error, screen failure data are to be recorded in the eCRF.

Rescreening does not apply to this study.

6.5. Meals and Dietary Restrictions

Not applicable.

7. STUDY DRUG(S) AND ADMINISTRATION

7.1. Investigational Medicinal Product

The IMP is defined as the investigational treatment IFX-1 and Placebo-to-match (Placebo) that is intended to be administered to a study patient according to the study protocol.

7.1.1. Packaging and Labelling of Investigational Medicinal Product

IFX-1 concentrate solution for infusion will be supplied in 20 mL glass vials at a concentration of 10 mg/mL (200 mg per vial) for reconstitution and IV administration. Apart from IFX-1, the solution will contain sodium chloride, sodium phosphate, and polysorbate 80.

Placebo concentrate solution for infusion will be supplied in 20 mL glass vials for reconstitution and IV administration. The solution will contain sodium chloride, sodium phosphate, and polysorbate 80.

IFX-1 and Placebo will be packaged in cartons and labeled in accordance with all legal requirements. Each carton will contain 4 vials of IFX-1 or 4 vials of Placebo. Each carton and each vial will be labeled with a multilingual booklet label or a single panel label as applicable.

7.1.2. Storage, Handling, and Accountability

Vials of IFX-1 and Placebo must be stored in a refrigerator at 2°C to 8°C (35.6°F to 46.4°F) in their original cartons to protect from light and must not be frozen or shaken. All supplies of IFX-1 and Placebo must be stored separately or segregated from other study supplies and site stock in a dedicated locked facility with access limited to authorized personnel. All storage facilities must be temperature controlled and monitored and compliant with applicable regulatory requirements.

An established and validated local temperature management system with temperature logs should be used to record the storage temperature. If this is not possible, the study site will be provided with a temperature record form by the Contract Research Organization (CRO) and the site personnel will maintain temperature records for the entire duration of the study. At a minimum, the daily (working day) minimum and maximum temperatures must be documented.

Any deviation from the specified temperature range must be documented and reported within 24 hours (or the next working day). Further instruction on the management and reporting of temperature deviations is provided in the Investigator Manual (or equivalent document).

The investigator or designee must confirm appropriate temperature conditions have been maintained during shipment for all IMP received and any discrepancies are reported and resolved before use of the IMP.

Only patients enrolled in the study may receive IMP and only authorized site staff may prepare and administer IMP. The IMP must be prepared in a controlled area in accordance with local regulations/ requirements for reconstitution of products for IV administration.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for the correct storage of IMP, IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IMP are provided in the Investigator Manual (or equivalent document) provided by the CRO.

7.1.3. Drug Preparation and Administration Instructions

The IFX-1 and Placebo for infusion will be reconstituted (prepared) in a controlled area at the study site or at the study site's pharmacy, in accordance (compliance) with applicable local regulations/ requirements for reconstitution of products for IV administration.

The reconstituted IFX-1 or Placebo should be used within 4 hours after dilution when stored at room temperature. Otherwise, the reconstituted IFX-1 or Placebo has to be stored at 2°C to 8°C (35.6°F to 46.4°F) and used within 24 hours; if the reconstituted solution is stored in a refrigerator, it must be left to acclimatize to room temperature prior to administration. Details for the preparation of the reconstituted solution will be provided in the Investigator Manual (or equivalent document).

The number of unused, partially used, and empty vials will be documented accurately, and the vials will be kept at the site until further notice by the Sponsor.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Further guidance and information for the final disposition of unused IMP are provided in the Investigator Manual (or equivalent document).

7.1.4. Recall of IMP

Instructions (actions to be taken by site) in the case of IMP recall are provided in the Investigator Manual (or equivalent document).

7.2. Administration and Dosage

For Phase II, patients were randomized to either receive BSC + IFX-1 in treatment Arm A or BSC alone in treatment Arm B. The first dose of IFX-1 was administered at Cycle 1 Day 1.

For Phase III, patients are randomized to either receive SOC + IFX-1 in treatment Arm A or SOC + Placebo in treatment Arm B. The first dose of IFX-1 or Placebo is administered at Day 1. SOC may start at any time according to their administration schedule.

Close observation of IFX-1 or Placebo infusion(s) is required for monitoring of potential infusion reactions. Appropriate treatment for potential infusion reactions must be available during this time.

7.2.1. Treatment Administered

7.2.1.1. Phase II

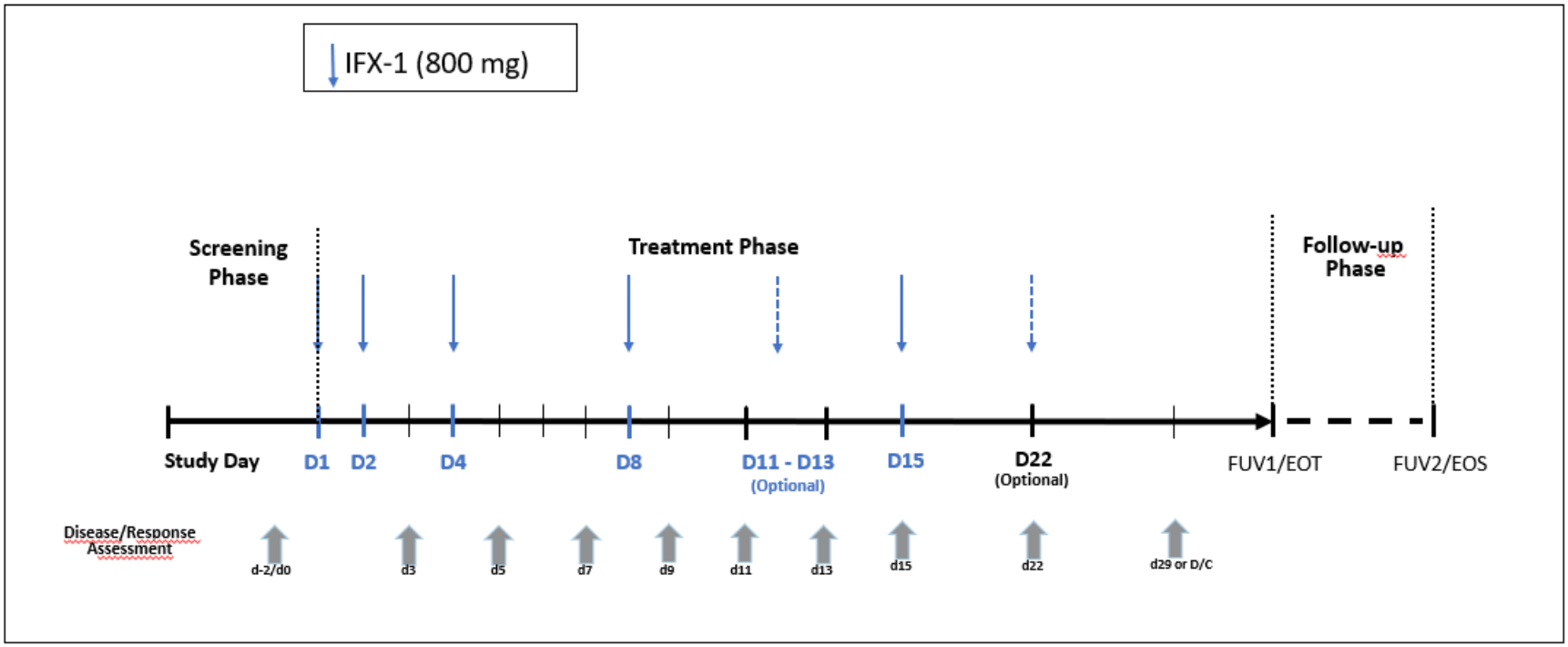
IFX-1 800 mg was administered for a maximum of 7 doses over a period of 29 days as a 30-minute IV infusion. However, given the variability of infusion pumps from site to site, a window between 5 minutes and +10 minutes was permitted (i.e., infusion time was 30 minutes (5 min/+10 min). IMP administrations for Phase II are detailed in Figure 1.

The first 5 treatments at days 1, 2, 4, 8, and 15 were administered to all patients randomized into Arm A. Treatment at day 22 was only administered in the event that a patient had not been extubated and discharged from ICU. In case a patient's clinical situation worsened after day 8, although an initial clinical benefit was observed, one additional administration of IFX-1 between day 11 and 13 could have been given at investigator discretion.

7.2.1.2. Phase III

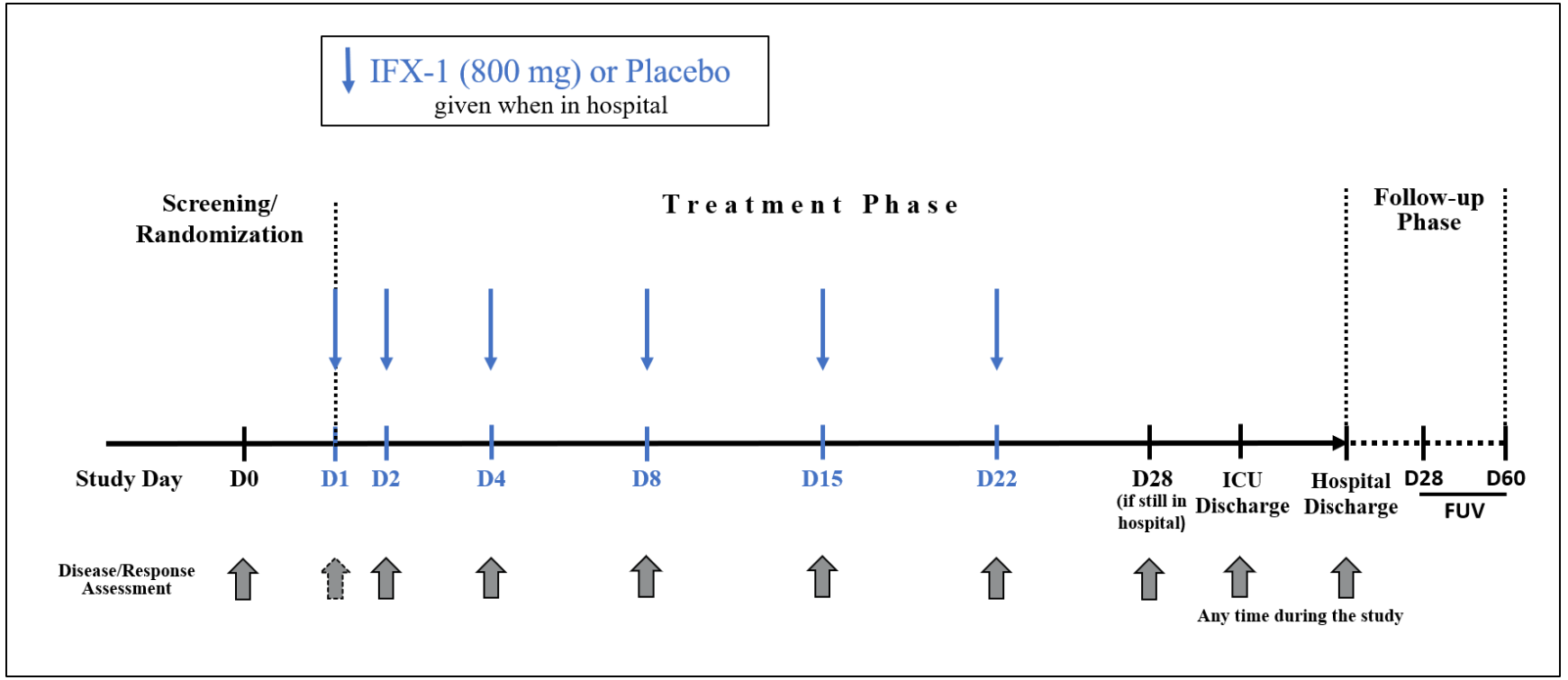
Patients will be treated with a maximum of 6 IV doses of IFX-1 800 mg (Arm A) or placebo (Arm B) administered as a 30-60-minute IV infusion. The 6 treatments are at days 1, 2, 4, 8, 15, and 22 as long as the patient is still in the hospital, even if discharged from ICU. IMP administrations for Phase III are detailed in Figure 2.

Figure 1 Patient Calendar: IMP Administrations – Phase II



D = day; D/C = discharge; EOS = end of study; EOT = end of treatment; FUV = follow-up visit; IMP = investigational medicinal product

Figure 2 Patient Calendar: IMP Administrations – Phase III



D = day; FUV = follow-up visit; ICU = intensive care unit; IMP = investigational medicinal product

7.2.2. Treatment Modification

This protocol allows some alteration from the currently outlined dosing schedule, but a dose reduction of IMP is generally not allowed.

Adverse events leading to treatment modifications will be graded as mild, moderate, severe, or life-threatening based on the investigator's assessment, using the definitions provided in Section 9.2.2.

In case of toxicity, IMP dosing can be held by a maximum of 1 week. If therapy is continued during this time span, dosing will resume at the initially planned next dosing day according to the initial schedule and allowed administration window.

For treatment discontinuation criteria, see Section 7.2.4.

7.2.2.1. Infusion Reactions

IFX-1 may cause infusion reactions, including severe or life-threatening hypersensitivity or anaphylactic reactions. Signs and symptoms of infusion reactions usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion with or without adequate medication. Dose modification criteria for infusion reactions are listed in Appendix 5, Table 6.

7.2.3. Re-dosing Criteria

The following criteria must be fulfilled to allow for re-dosing of study drug:

- Absence of treatment discontinuation criteria (see Section 7.2.4).

7.2.4. Treatment Discontinuation Criteria

Discontinuation of study treatment does not represent withdrawal from the study. See Section 5.6.1.1 (for Phase II) or Section 5.6.2.1 (for Phase III) for the end of treatment definition and procedures.

In general, patients should be treated with IMP until unacceptable toxicity, completion of the planned treatment, or death.

Possible reasons for treatment discontinuation for individual patients are:

- Clinical deterioration
- Study participation consent withdrawal (see Sections 5.6.1.3 and 5.6.2.3)
- Transfer of patient to another hospital

- Safety:
  - moderate infusion reactions despite adequate premedication (see Appendix 5, Table 6)
  - severe or life-threatening infusion reactions (see Appendix 5, Table 6)

7.3. Premedication and Postmedication

Routine premedication is not required prior to the first dose of IMP.

Patients with mild or moderate infusion reaction following IMP administration may continue to receive IMP with close monitoring; premedication with antipyretic and antihistamine may be considered.

Patients should be observed for 60 minutes, or longer per clinical judgment, after IMP administrations.

Treatment guidelines in case of occurrence of infusion reactions are detailed in Appendix 5, Table 6.

7.4. Prior and Concomitant Medication/Treatments

In Phase III of the study, in addition to the IMP, all patients will receive SOC for treatment of COVID-19, which includes VTE prophylaxis with anticoagulants at a minimum. Other international or country-specific recommended treatments for COVID-19 per the locally adopted treatment recommendations (including but not limited to corticosteroids, remdesivir, and other local SOC) are allowed as concomitant medications. SOC treatment start and stop is not defined by the protocol and can start at any time. SOC treatment will be given according to investigator's discretion.

Reporting of prior and concomitant medications will follow special considerations for the ICU setting, as described in Appendix 12.

Reportable medications or vaccinations that the patient is receiving within 7 days prior to randomization and up to 30 days after the last dose of study treatment should be recorded along with:

- Reason for use
- Dates of administration including start and end dates

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.4.1. Prohibited Concomitant Medication/Treatment

Medications or vaccinations specifically prohibited in the exclusion criteria (see Sections 6.1.2 and 6.2.2) are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy may be required. The investigator should discuss any questions regarding this with the medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on study treatment requires the mutual agreement of the investigator and the sponsor.

The following concomitant therapies or vaccinations are prohibited during the course of the study:

- Antineoplastic systemic therapy
- Investigational antibody treatments and other investigational agents (excluding IFX-1 but including SARS-CoV-2 multiplication inhibitor[s] or immunomodulator[s]) which are not approved or not included in locally adopted treatment recommendations for treatment of COVID-19 (e.g., WHO guidance, NIH COVID-19 treatment guidelines)
- Cytokine adsorption therapy

Patients who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study.

All treatments that the investigator considers necessary for a patient’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

7.5. Rescue Medications and Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator.

7.6. Treatment of Overdose

No specific information is available on the treatment of overdose of IFX-1. For this study, an overdose of IFX-1 will be defined as any single dose of > 1,200 mg. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately
2. Closely monitor the patient for any AE/SAE and laboratory abnormalities

3. Obtain a plasma sample for PK analysis as close as possible to the administration of overdose if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the patient.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Phase II

Study procedures and their timing for Phase II are summarized in the Schedule of Assessments (SoA; Table 1).

Details on the assessments and procedures are given in the following subsections.

Safety concerns should have been discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue any IMP.

Adherence to the study design requirements, including those specified in the SoA (Table 1), was essential and required for study conduct.

All screening evaluations must have been completed and reviewed to confirm that potential patients met all eligibility criteria (Section 6.1). The investigator was to maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1.1. Baseline Assessments

The following procedures were to be performed to assess baseline characteristics during screening evaluations and before IMP administration:

- Documentation of demographic details (age, gender, race, and ethnicity), medical and disease history (see Sections 8.1.1.1 and 8.1.1.2)
- Disease assessments (see Section 8.1.2)
- Documentation of concomitant disease and concomitant medications (see Sections 8.1.1.3 and 8.1.1.4)
- Baseline safety assessment (height, weight, physical exam, vital signs, AEs, and safety laboratory; see Section 8.1.3)

8.1.1.1. Medical History (Except COVID-19 history)

The documentation of the patient's medical history were to include any details on the patient's medical history before enrollment into the study. The information must have been documented as such in the source documentation and eCRF.

8.1.1.2. COVID-19 History

Any details on the patient's COVID-19 disease history including any COVID-19 therapy (onset of symptoms, medications, oxygen support, intubation, SARS-CoV-2 testing) by verbatim name with start and end dates, dosages, modality) that the patient received were to be documented in the source documentation and in the eCRF.

8.1.1.3. Concomitant Disease

All diseases that the patient was experiencing at enrollment into the study or after enrollment until EOT were to be regarded as concomitant diseases. All concomitant diseases must have been documented in the source documentation and in the eCRF.

8.1.1.4. Prior and Concomitant Medications

All drugs being taken by a patient at enrollment into the study or after enrollment until EOT were to be regarded as concomitant medication.

All prior medications taken by the patient within 2 weeks before enrollment into the study and all concomitant medications must have been documented in the source documentation and in the eCRF. Details on prior and concomitant medications must have included the reason for use, administration start and stop dates, and dosing information, including dose, route, and frequency of administration.

8.1.2. Efficacy Assessments

8.1.2.1. Imaging Requirements

CT scan, MRI, or X-ray for COVID-19 assessment were to be performed locally at each scheduled disease assessment time point, and at any time when disease progression was suspected.

The choice of whether the imaging was by CT scan, MRI, or X-ray was an investigator decision. Once the imaging choice had been made, subsequent assessments should have been made using the same modality whenever possible.

8.1.2.2. Evaluation of Lung Function

- Oxygenation index (PaO_2 / FiO_2)
- Respiratory rate
- Oxygen supplementation: room air, flow O_2 (L/min) if extubated

- Ventilation status (invasive/non-invasive/intermittent non-invasive)
- Mode of ventilation (e.g., CPAP/BIPAP)
- Other oxygenation support
    - Type of oxygen mask or nasal canula, or other mechanical ventilation mode and parameters, as applicable, should have been documented
- Intubation and extubation dates, as well as date of tracheostomy should have been documented

8.1.2.3. Evaluation of Response

- SARS-CoV-2 mRNA testing was to be performed in context of enrolment procedures and at one to four additional time points at discretion of the investigator

8.1.2.3.1. Evaluation of Early Response

Early Response as defined as meeting ALL of the following criteria at day 7 after enrollment:

- Patient alive and extubated OR oxygenation index ≥ 300 OR improvement of ≥ 30% from baseline,
- Temperature < 38°C in absence of fever decreasing medication of at least 4h
- White blood cell count within normal limit of local lab quantifications

8.1.2.3.2. Evaluation of Late Response

Late Response as defined by either being **discharged alive** from hospital until day 28 **OR** meeting **ALL** of the following criteria at day 28 of the trial:

- Patient alive and extubated
- Patient discharged from ICU
- Patient free of shortness of breath (respiratory rate < 20) in absence of oxygen supply
- Patient free of fever (< 37.6°C)

8.1.3. Safety Assessments

Safety was to be assessed based on the following variables:

- AEs (see Section 8.1.3.1)
- Laboratory safety parameters (see Section 8.1.3.2)
- Vital signs (see Section 8.1.3.3)
- Electrocardiograms (see Section 8.1.3.4)
- Physical examination (see Section 8.1.3.5)

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.1.3.1. Adverse Events Assessments

Adverse events were to be assessed throughout the study from the time of enrollment to the EOT visit as specified in the SoA (Table 1). For details on AE collection and reporting, see Section 9.1. The investigator should have taken appropriate measures to follow all AEs until clinical recovery was complete and laboratory results had returned to normal, or until progression had been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations would continue beyond the last planned visit per protocol, and that additional investigations may have been requested by the sponsor. When study treatment was prematurely discontinued, the patient's observation was to be continued until the EOT visit for that patient as defined by the protocol.

8.1.3.2. Clinical Safety Laboratory Assessments

In general, blood samples for safety laboratory analysis should have been obtained once a day during a routine sampling (preferable in the morning) before administration of IMP. Additional tests may have been performed at any time during the study as determined necessary by the investigator or required by local regulations.

See Appendix 1, Table 3 for the list of clinical laboratory tests performed and the SoA (Table 1) for timing and frequency.

The investigator must have reviewed the laboratory report, documented this review, and recorded any clinically relevant changes (clinically relevant abnormal findings) occurring during the study in the AE section of the eCRF. The laboratory reports must have been filed with the source documents. Clinically relevant abnormal laboratory findings were those which were not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically relevantly abnormal and with onset before EOT visit should have been reported in the AE section of the eCRF and repeated until the values returned to normal or baseline, were no longer considered clinically relevant by the investigator or medical monitor, or until the EOS visit (also see Section 8.1.4 and Appendix 3).

If such values did not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should have been identified, and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 1, Table 3, must have been conducted in accordance with the SoA (Table 1).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory required a change in patient management or were considered

clinically relevant by the investigator (e.g., SAE or AE or dose modification), then the results must have been recorded in the eCRF.

Blood samples for serum pregnancy testing were to be collected on the same day as safety laboratory testing. For details on pregnancy testing, refer to Appendix 4.

8.1.3.3. Vital Signs

Core body temperature, heart rate, respiratory rate, and blood pressure (diastolic and systolic) were to be assessed at each visit at pre-dose on the days of IMP administration and at further time points whenever medically indicated.

Blood pressure and pulse measurements were to be assessed with a completely automated device. Manual techniques were to be used only if an automated device was not available.

Vital signs were to be measured in a supine position (after a rest of at least 1h in case of position switch from prone position), preferably in the morning. Three readings of blood pressure and pulse were to be taken. The first reading should have been rejected. The second and third readings should have been averaged to give the measurement recorded in the eCRF.

8.1.3.4. Electrocardiograms

12-lead electrocardiogram (ECG) was to be obtained as outlined in the SoA (Table 1) using an ECG machine that automatically calculated the heart rate and measured PR, QRS, QT, and QTc intervals.

8.1.3.5. Physical Examination

A physical examination was to be conducted at screening and each study visit.

The physical examination included, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (at screening) and weight was also to be measured and recorded as specified in the SoA (Table 1).

Investigators should have paid special attention to clinical signs related to previous serious illnesses.

8.1.3.6. Survival Status

The patient survival status were to be assessed during the study and follow-up and documented in the eCRF. In case the patient died and the date of death was unknown, the date of the last personal contact should have been documented at a minimum.

8.1.4. Pharmacokinetics/Pharmacodynamics

If possible, blood samples were to be collected pre-dose for measurement of plasma concentrations and C3a and C5a of IFX-1 as specified in the SoA (Table 1). IFX-1 concentrations were to be measured for all patients in citrate plasma and analyzed by a specialized laboratory using Enzyme-Linked ImmunoSorbent Assay.

Detailed instructions regarding the collection, processing, etc., of samples were to follow local regulations and requirements.

8.1.5. Biobanking of Samples from Patients Treated at Amsterdam Medical Center

COVID-19 is a new viral disease with distinct clinical and pathophysiological features, which differentiate COVID-19 from other viral diseases such as Influenza. A COVID-19 dedicated Biobank was established at the Amsterdam Medical Center (AMC) in order to investigate further COVID-19 pathophysiological characteristics. Therefore, it was planned to store all remaining AMC study patient derived biomaterials, including but not limited to blood, bronchial lavage fluid, and tissue in the AMC COVID-19 Biobank. Patients were to be asked for a separate informed consent.

8.2. Phase III

Study procedures and their timing for Phase III are summarized in the SoA (Table 2).

Details on the assessments and procedures are given in the following subsections.

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue any IMP.

Adherence to the study design requirements, including those specified in the SoA (Table 2), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria (Section 6.2). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.2.1. Baseline Assessments (Screening)

The following procedures will be performed to assess baseline characteristics during screening evaluations and before randomization and IMP administration:

- Check inclusion and exclusion criteria

- Documentation of demographic details (age, gender, race, and ethnicity), medical and COVID-19 history (see Sections 8.2.1.1 and 8.2.1.2). Race information is required for eGFR calculation using the CKD-EPI equation
- 8-point ordinal scale assessment (see Section 8.2.2.2) and oxygenation index (PaO_2 / FiO_2; one representative measurement within 6h before randomization)
- Documentation of concomitant disease and prior medications (see Sections 8.2.1.3 and 8.2.1.4)
- Baseline safety assessment (height, weight, physical exam, AEs, ECG, urine analysis, pregnancy test, and clinical safety laboratory [including creatinine assessment]); see Section 8.2.3)

8.2.1.1. Medical History (Except COVID-19 History)

The documentation of the patient's medical history includes any details on the patient's medical history before randomization into the study. The information must be documented as such in the source documentation and eCRF.

8.2.1.2. COVID-19 History

Any details on the patient's COVID-19 disease history including any COVID-19 therapy (onset of symptoms, medications, oxygen support, intubation and tracheostomy dates, SARS-CoV-2 polymerase chain reaction (PCR) test date and result by verbatim name with start and end dates) that the patient received will be documented in the source documentation and in the eCRF.

8.2.1.3. Concomitant Disease

All diseases that the patient is experiencing at screening/randomization until end of treatment are regarded as concomitant diseases. All concomitant diseases must be documented in the source documentation and in the eCRF.

8.2.1.4. Prior and Concomitant Medications and Procedures

All procedures performed or medications administered within 7 days before randomization should be recorded as prior procedures and prior medication with generic name, start date, stop date, and indication for treatment.

Reporting of prior and concomitant medications will follow special considerations for conditions in the ICU. A complete record of all prior and concomitant medications (but excluding nutritional and volume therapy, electrolyte support, vitamins, non-steroidal anti-inflammatory drugs (NSAIDs), and supportive therapies such as artificial tears, ointments, stool softeners/laxatives, etc.) will be maintained in the eCRF for each participant, beginning 7 days before randomization and continuing up to 30 days after the last dose of study treatment).

In addition, a complete record of all steroid and antibiotic therapy, as well as any therapy (medications, specific treatments, etc.) associated with or used in the assessment or treatment of an AE will be documented for the duration of the study.

The following information must be recorded in the eCRF for each reportable concomitant medication: generic name, route of administration, start date, stop date, and indication (Appendix 12).

8.2.2. Endpoint Assessments

8.2.2.1. Evaluation of Organ Support

- Renal replacement therapy, extracorporeal membrane oxygenation (ECMO), mechanical ventilation
- Extubation and re-intubation dates should be documented

8.2.2.2. Ordinal Scale Evaluation

8-point ordinal scale score will be documented at the visits specified in the SoA (Table 2), including the date (one value per assessment day, that best represents the patient's condition at that day).

8.2.2.3. Survival Status

The patient's survival status will be assessed during the study and at the day 28 and day 60 FUV and will be documented in the eCRF. In case the patient has died and the date of death is unknown, the date of the last personal contact should be documented at a minimum.

8.2.2.4. Quality of Life Assessment

Patients will be assessed for quality of life using the EQ-5D at the day 60 FUV.

8.2.2.5. Clinical Status

Patient's clinical status will be assessed by the Glasgow Outcome Scale at the day 60 FUV.

8.2.3. Safety Assessments

Safety will be assessed based on the following variables:

- AEs (see Section 8.2.3.1)
- Laboratory safety parameters, including creatinine (see Section 8.2.3.2)
- Vital signs (see Section 8.2.3.3)
- Electrocardiograms (see Section 8.2.3.4)
- Physical examination (see Section 8.2.3.5)

Planned time points for all safety assessments are provided in the SoA (Table 2).

8.2.3.1. Adverse Events Assessments

Adverse events will be assessed throughout the study as specified in the SoA (Table 2). Adverse event reporting will follow special considerations for the ICU setting as described in Appendix 3.

8.2.3.2. Clinical Safety Laboratory Assessments

In general, blood samples for safety laboratory analysis and creatinine assessment should be obtained at indicated visit days during routine sampling (one representative value, if taken more than once a day). Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

See Appendix 1, Table 4 for the list of clinical laboratory tests to be performed and the SoA (Table 2) for timing and frequency.

In clinical studies conducted in the ICU, deviations in laboratory values are to be expected frequently. Clinical judgement should be applied in determining which deviations should be reported as an AE in the sense of an "untoward medical occurrence" and which deviations should be considered usual and expected findings in this setting.

It must be noted that clinically significant laboratory deterioration as assessed by the investigator with onset before end of treatment must be documented in the respective eCRF section. However, it is preferred to document the condition or disease underlying the aberrant laboratory value (e.g., renal failure rather than hyperkalemia) rather than the laboratory value only.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant, and thus constitutes an AE (see also Section 9 and Appendix 3).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory fulfill the aforementioned criteria for clinical significance, then the results must be recorded in the eCRF.

All protocol-required laboratory assessments, as defined in Appendix 1, Table 4, must be conducted in accordance with the SoA (Table 2). Please note that day 1 safety laboratory assessment, including creatinine assessment, has to be done prior to IMP administration only, if more than 12 h elapsed between the screening assessment and the IMP administration.

Urine analysis and serum or urine samples for pregnancy testing will be collected only at screening/randomization. For details on pregnancy testing, refer to Appendix 4.

8.2.3.3. Vital Signs

Vital signs (core body temperature, heart rate, respiratory rate, blood pressure [diastolic and systolic]) will be assessed at indicated visits at pre-dose within 1h before administration of IMP (one representative measurement closest to IMP administration) and at further time points whenever medically indicated. Blood pressure and heart rate measurements will be assessed with an intra-arterial catheter, or a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3.4. Electrocardiograms

12-lead ECG will be obtained as outlined in the SoA (Table 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

8.2.3.5. Physical Examination

A physical examination will be conducted at the time of screening/randomization, on day 1 prior to IMP administration only, if more than 24 h elapsed between screening assessment and IMP administration, and on the days of further IMP administration, as specified in the SoA (Table 2).

The physical examination includes, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems.

8.2.4. Pharmacokinetics/Pharmacodynamics

PK/PD testing will be done at selected countries/sites. Blood samples will be collected for measurement of plasma IFX-1 concentrations, C5a, and ADAs of IFX-1 within 1h before administration of IMP, as specified in the SoA (Table 2).

Detailed instructions regarding the collection, processing, etc., of samples will follow local regulations and requirements.

9. ADVERSE EVENT COLLECTION AND REPORTING

All AEs, serious and non-serious (see Appendix 3 I for definitions), must be collected, documented, and reported from signature of the informed consent or, where informed consent is deferred, from the documented decision timepoint of the responsible investigator and/or physicians to enroll the patient until the end of treatment (see Section 9.1.1). They will be further followed up until the end of study (see Section 9.1.1.1), however death and related SAEs with onset during the follow-up period and after the end of study will be collected and reported (see Section 9.1.2).

All AEs will be reported to the sponsor by the investigator in the appropriate sections of the eCRF. It will be specified whether the event is serious or not according to the definition of SAE (see Appendix 3 I). In case of an SAE, the SAE report will be processed by the safety vendor

(see Section 9.2.1). The safety vendor for this study is IQVIA Pharmacovigilance. Reporting of AEs will be done according to the specific definitions and instructions for completing the respective sections of the eCRF.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE and remain responsible for following up AEs, considered related to the IMPs or study procedures (see Section 9.2.2 and Appendix 3 II for details on causality of AEs), or that caused the patient to discontinue study treatment (see 7.2.4 for treatment discontinuation criteria) or the study.

Care will be taken not to introduce bias when detecting AEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

Due to the severity of disease of the patient population entering this study, numerous problems, signs, and symptoms deviating from normal will be seen during the course of the study. These will not necessarily constitute a reportable AE unless they require significant intervention, lead to discontinuation of blinded study drug, or are considered to be of concern in the investigator's clinical judgement. Similarly, it is preferred to receive documentation of the underlying condition rather than the resulting sign (e.g., 'agitation' rather than 'self-extubation').

In clinical studies conducted in the ICU, deviations, e.g., in laboratory values or temporary changes in arterial blood pressure, are to be expected frequently. Clinical judgement should be applied in determining which deviations should be reported as an AE in the sense of an "untoward medical occurrence" and which deviations should be considered usual and expected findings in this setting. It is preferred to document the condition or disease underlying the aberrant laboratory value (e.g., renal failure rather than hyperkalemia) rather than the laboratory value only.

The records will describe (Appendix 3 II) the nature (diagnosis or single syndrome if possible, alternatively signs and symptoms), severity (mild, moderate, severe, life-threatening, fatal), start date and time, stop date and time, actions taken with respect to the IMP, corrective treatment/therapy given, additional investigations performed, outcome, and causality (relationship to study treatment according to the investigator's assessment; see also Section 9.2.2).

The terms 'disease progression', 'progressive disease', or similar, do not constitute an acceptable description of the nature of an AE. For example, if a patient experiences disease progression with hemoptysis leading to hospitalization, the investigator should file an AE and an SAE for the hemoptysis; data related to disease progression should be captured in the disease assessment and response evaluation section of the eCRF.

Any AE not listed as an expected event in the IB or in this protocol will be considered unexpected.

9.1. Time Period and Frequency of Collection and Reporting

The following timeframes for reporting apply from signature of the informed consent or, where informed consent is deferred, from the documented decision timepoint of the responsible investigator and/or physicians to enroll the patient, on:

- All AEs, including AESIs and SAEs until 30 days following the last IFX-1 administration must be reported
- All pregnancies until 30 days after the last dose of treatment with IFX-1 must be reported until completion of the pregnancy, as described in Section 9.5.2

Any time outside of the time period specified above, in addition, any study drug-related SAEs brought to the attention of an investigator must be reported immediately to the sponsor.

9.1.1. During Treatment

All AEs, including SAEs and AESIs, must be collected and reported appropriately from the time of patient/others signing the consent form or, where informed consent is deferred, from the documented decision timepoint of the responsible investigator and/or physicians to enroll the patient until 30 days following the last IFX-1 administration.

- All AEs must be followed until the outcome of the event is 'recovering' (for stabilization of chronic conditions), or recovered (/with sequelae), and until all queries related to these AEs have been resolved.
- Ongoing AEs should be reviewed at each scheduled and unscheduled visit until the hospital discharge visit. All details should be recorded in the eCRF. If any AE changes for the worse, in frequency of attacks/symptoms or in severity, a new record of the event must be started (i.e. distinct reports are required for differing frequencies and/or severity of the same event to enable comprehensive safety reports and later analysis).
- If the patient dies from an event, ongoing further AEs can be closed with an outcome 'unknown', if outcome was not assessed at day of death.

9.1.1.1. During Follow-up

All ongoing AEs with onset in the treatment period will have to be followed up after the hospital discharge visit until the outcome of the event is 'recovering' (for chronic conditions), or recovered (/with sequelae), or until end of study and until all queries related to these AEs have been resolved.

All SAEs, including fatal events, related to IMP with onset during the follow-up period (from the hospital discharge visit until end of study) will have to be collected and followed until resolved.

9.1.2. After End of Study

After the end of study, new SAEs related to IMP must be reported to the sponsor via the regular SAE reporting system.

9.2. Serious Adverse Event Reporting and Timelines

9.2.1. Initial Reporting of Serious Adverse Events

SAEs that should be reported within 24 hours on the SAE form are:

- Events with fatal outcome
- New life-threatening events, defined as:
  - Cardiac event requiring CPR or medical resuscitation (adrenaline use etc.) – can be caused by severe arrhythmia or other
  - Life-threatening spontaneous bleeding requiring blood transfusion and / or surgical intervention
  - Thrombo-embolic event with life-threatening hemodynamic or pulmonary instability
  - New life-threatening organ failure / dysfunction
    - Liver: AST, ALT > 20 x upper limit of normal (ULN) OR Bilirubin > 10 x ULN
    - Kidney: Creatinine > 6 x ULN – or newly developed anuria ≤ 100 mL urine production over 24h
    - Cardiovascular:
      - Norepinephrine > 1 µg/kg/min or equivalent
      - Troponin I: levels consistent with myocardial infarction as defined by manufacturer
    - Coagulation: Thrombocyte count < 20.000 / µL or partial thromboplastin time (PTT) > 2.5 x ULN
  - Life-threatening infections other than COVID-19 which require immediate antibiotic treatment and/or additional medical / surgical intervention
  - Life-threatening infusion reactions which require immediate intensification of existing intensive care treatment, including but not limited to additional vasopressor of fluid support, or high dose corticosteroids and antihistamines

All remaining SAEs should be reported at investigator's earliest convenience. SAEs should be approved by the investigator (see Appendix 3 II). In addition, SAEs need to be reported in the (non-serious) AE section of the eCRF. The investigator will be requested to supply as much detailed information regarding the event as is available at the time of the initial contact.

For transmission of the back-up paper-based SAE form, please use the following FAX line or e-mail account:

Fax: +353 1 809 9501

QLS_IFX1@iqvia.com

In addition, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical study are properly mentioned on any copy of a source document provided to the sponsor. For laboratory results, the investigator must include the laboratory normal ranges.

9.2.1.1. Follow-up Reporting of Serious Adverse Events

Follow-up information on SAEs must be reported by the investigator within the same time frames as the initial reporting.

A follow-up report to an SAE should be prepared if any relevant change in the condition of the patient occurs after the initial report, or any new relevant information becomes available.

Further information on follow-up procedures is given in Appendix 3 II.

9.2.2. Determination of Relatedness

The investigator will use medical consideration to determine the relatedness of an AE with the study drug based on the following definitions (see also Appendix 3 II):

Unrelated

This category applies to AEs that are due to extraneous causes (disease, concomitant medication, environment, etc.) and are not related to the administration of study drug.

Unlikely Related

This category applies to AEs that are unlikely related to the administration of the study drug. The relationship of an AE to the study drug can be considered unlikely related if (must have first two criteria listed below):

- The AE does not follow a reasonable temporal sequence from administration of the drug
- The AE could readily have been a result of the patient’s clinical state or other underlying medical condition, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE does not follow a known response pattern to the suspected drug
- The AE does not reappear or worsen when the study drug is re-administered

Possibly Related

This category applies to AEs that are unlikely to be related to the administration of the study drug, but the possibility cannot be ruled-out with certainty. The relationship of an AE to the study drug can be considered possibly related if (must have first two criteria listed below):

- The AE follows a reasonable temporal sequence from administration of the study drug
- The AE could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE follows a known response pattern to the suspected study drug

Probably Related

This category applies to AEs that are considered with a high degree of certainty to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered probably related if (must have first three criteria listed below):

- The AE follows a reasonable temporal sequence from administration of the study drug
- The AE could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE disappears or decreases upon cessation of study drug or reduction in dose
- The AE follows a known response pattern to the suspected study drug

Definitely Related

This category applies to AEs that are determined with certainty to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered definitely related if (must have first three criteria listed below):

- The AE follows a reasonable temporal sequence from administration of the study drug or study drug levels have been established in body fluids or tissues
- The AE could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The AE disappears or decreases upon cessation of study drug or reduction in dose and, if applicable, appears upon re-challenge
- The AE follows a known response pattern to the suspected study drug
- There are exceptions when an AE does not disappear upon discontinuation of the study drug, yet study drug relatedness clearly exists; e.g., 1) tardive dyskinesia, 2) fixed drug eruptions

9.3. Death Reporting

The site should follow all patients for survival and collect information around the death on the appropriate eCRF form until the end of the study.

Primary cause of death should be reported in AE section and SAE form, as well as appropriate eCRF section(s). If symptoms of disease progression occurred and constitute the primary cause of death, these symptoms could be reported as fatal (S)AE (see Section 9.2.2).

9.4. Abnormal Laboratory Values/Vital Signs/ECG/Physical Examination

Abnormalities of laboratory results / vital signs / ECG / physical examination should be reported as AEs, particularly if at least one of the following is met:

- Any criterion for an SAE is fulfilled
- The abnormality causes the patient to discontinue from the study treatment
- The abnormality causes the patient to interrupt the study treatment or a modification of dosing
- The abnormality requires intervention as corrective treatment or consultation
- The investigator judges that the abnormality is clinically significant and should be reported as an (S)AE in the eCRF

All laboratory tests for which clinically significant abnormal results are observed after the initiation of study treatment should be repeated until the values return to normal or to a stable status. Clinically significant abnormal laboratory results must be reported as an AE. The frequency with which such checks should be made will be made by investigator's discretion depending on the degree of abnormality. The reporting of laboratory/vital signs/ECG/physical examination abnormalities as both AEs and a specific finding of laboratory values/vital signs/ECG should be avoided.

Abnormal laboratory value testing will follow special considerations for conditions in the ICU (refer also to Appendix 3, III Special Considerations for Assessment of Adverse Events in an ICU Setting). It must be noted that clinically significant laboratory deterioration as assessed by the investigator must be documented in the respective eCRF section. However, it is preferred to document the condition or disease underlying the aberrant laboratory value (e.g., renal failure rather than hyperkalemia) rather than the laboratory value only.

9.5. Events to be Handled as SAEs

9.5.1. Overdose Reporting

An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically relevant.

All symptoms associated with the overdose should be handled as SAEs.

Refer to Section 7.6 for details on the treatment of overdose.

9.5.2. Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant during treatment or within 30 days after the last dose of treatment with IFX-1, the investigator should report the pregnancy to QLS_IFX1@iqvia.com via e-mail within 24 hours of being notified. The safety vendor will then forward the pregnancy reporting form to the investigator for completion. In case that e-mail contact is not possible, the site can provide an initial pregnancy report in the SAE section of the SAE form and transmit this via the SAE FAX line: +353 1 809 9501.

A patient becoming pregnant while on IMP will immediately be discontinued from treatment and the EOT visit will be performed.

The patient or partner should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the sponsor. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting as SAE.

9.5.3. Drug-induced Liver Injury

Potential drug-induced liver injury is considered an important medical event. Although it is not always serious by regulatory definition, such event must be handled as SAE.

Wherever possible, timely confirmation within 48 to 72 hours of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury event. All occurrences of potential drug-induced liver injuries, meeting the defined criteria, must be reported as SAEs.

Potential drug-induced liver injury is defined as:

- ALT or AST elevation > 3 × ULN

AND

- Total bilirubin >2 × ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

- No cholestatic or other immediately apparent possible causes of AST or ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

9.5.4. Suspected Transmission of an Infectious Agent (Pathogenic or Non-pathogenic) via Study Drug

For the purposes of reporting, any suspected transmission of an infectious agent via the investigational drug should be considered as an SAE.

A transmission of an infectious agent may be suspected from clinical signs or symptoms, or laboratory findings indicating an infection in a patient exposed to a medicinal product.

In the context of evaluating a suspected transmission of an infectious agent via a medicinal product, care should be taken to discriminate, whenever possible, between the cause (e.g., injection/administration) and the source (e.g., contamination) of the infection and the clinical conditions of the patient at the time of the infection (immuno-suppressed /vaccine).

9.6. Adverse Events of Special Interest

AESIs are events that are considered to have a special meaning or importance for a particular drug or class of drugs. They may be non-serious or serious. Therefore, they should be closely monitored. The site must report all AESIs that occur during the study period, whether considered to be related to IP or not, according to Appendix 3. Moreover, AESIs should be documented in the general AE section of the eCRF as well as in the patient file.

This is the first study investigating IFX-1 in COVID-related pneumonia. Clinical experience with IFX-1 has been generated in more than 300 patients with inflammatory diseases, including sepsis and HS.

For this study, the following AEs are defined as AESIs:

- Infusion reactions, including hypersensitivity or anaphylaxis during or after IFX-1 infusion:

  All patients should be observed closely during the IFX-1 administration and for ≥ 60 minutes thereafter. The intravenous line should remain open during the observation to allow for administration of intravenous drugs, if necessary. Medication for infusion reactions should be available for immediate use. Medical staff has to be trained in resuscitation and immediate intensive care has to be easily accessible in case of severe life-threatening events. Mild to moderate reactions may be treated by slowing or interruption of the infusion, or with supportive treatment (Appendix 5).

  For any potential infusion event, the investigator should closely monitor for a potentially developing or existing anaphylactic reaction. In case an anaphylactic reaction is anticipated, appropriate immediate actions should be taken according to the severity or stage of the detected anaphylactic reaction.

- Meningitis and meningococcal sepsis:

In case of signs of meningitis at any time during the study, the IMP should be discontinued if meningitis is confirmed. The patient must be closely monitored and the guidelines for treatment of meningitis should be followed (Tunkel et al. 2004, van de Beek et al. 2016). This includes lumbar puncture, blood culture testing, immediate start of treatment with dexamethasone and intravenous antibiotics (combination therapy with ampicillin and third generation cephalosporin), and a search for the focus of the infection (e.g., CT or MRI).

- Infections other than COVID-19 (SARS-CoV-2) infections

  In patients with bacterial infection, depending on the severity of the infections, it is important that concomitant antibiotic therapy is administered during treatment with IFX-1 to ensure appropriate control of the source of the infection. The investigator should pay close attention to the choice of an appropriate broad-spectrum antibiotic treatment according to applicable guidelines.

  Note: A severe infection can be suspected whenever an IV antibiotic, antifungal, or antiviral intervention would be indicated under non-ICU conditions or an invasive intervention would have been indicated.

9.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Disease progression does not constitute an AE itself; however, the symptoms/diagnosis leading to disease progression must be reported as AE or SAE accordingly.

9.8. Reporting to Competent Authorities and Ethics Committees

The IB(s) will be the reference document for reference safety information.

The safety vendor is responsible for submission of suspected unexpected serious adverse reactions (see Appendix 3 I for a definition) to health authorities and Institutional Review Boards (IRB)/Independent Ethic Committees (IEC) in accordance with local regulations.

The investigator is responsible for informing the IRB/IEC in a timely manner and in accordance with local procedures.

10. STATISTICAL CONSIDERATIONS

10.1. Phase II

10.1.1. Sample Size Determination

No formal sample size calculation was performed for this trial. The sample size was based on pragmatic considerations in this new and urgent setting with very limited knowledge about the disease.

For the Phase II part of the trial 30 patients were randomized in a 1:1 ratio to treatment Arm A (SBC + IFX-1) and Treatment Arm B (BSC).

10.1.2. Analysis Sets

All analyses were to be performed based on all randomized patients.

10.1.3. Statistical Analyses

The statistical analysis plan (SAP) was developed and finalized as soon as possible after clinical trial application approval. The SAP includes the exact definition of endpoints and variables to be analyzed, extensive details on the statistical analysis methods to be used together with the structure of tables and figures to be included as end-of-text tables and figures as well as appended listings for the clinical study report. It also describes procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints for Phase II of this study.

Individual data were to be listed. Data were to be summarized using suitable descriptive statistics; depending on the structure of the data, summary statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) or frequency tables may have been used.

All data were to be displayed by treatment arm if not specified otherwise.

10.1.3.1. Efficacy Analyses

The relative change (%) from baseline (day 1 prior to study drug administration at ± 1h of randomization) in oxygenation index (PaO_2 / FiO_2) in supine position at day 3, 5, 9, and 15 was to be analyzed with a linear repeated measures model with post-baseline time points as outcome variable and baseline value as explanatory variable. Deceased patients were to be included in the model with an outcome of 0 after death. Patients discharged from the ICU whose oxygenation index was no longer be assessed were to be analyzed by last observation carried forward. Treatment arm, time point, the interaction between treatment arm and time point, the interaction between baseline and time point, age, sex, and intubation status at baseline was to be included as further explanatory variables. The model was to use an unstructured covariance matrix and make use of the Kenward-Roger degrees of freedom approximation. Least square mean differences between treatment arms and their 95% confidence interval was to be calculated and displayed for each time point separately (day 3, 5, 9, and 15), with the evaluation at day 5 reflecting the primary endpoint. If oxygenation index was to be used as the primary endpoint for a Phase III part of the study, data from both study parts were planned to be analyzed in one combined model as specified above with study part as a random effect.

Early response, late response and reaching ICU discharge alive were to be analyzed as three separate time-to-event variables. Withdrawing early from the study would have led to the patient

being right-censored at the date of withdrawal provided that the reason was not an outcome of interest for the time-to-event endpoint. In order to adequately account for competing outcomes as well as potential right-censoring due to varying follow-up times, these outcomes were to be non-parametrically analyzed using Aalen-Johansen-type estimation based on a competing risks model with two absorbing states (event 1: all-cause death; event 2: early response/late response/ICU discharge respectively). The Aalen Johansen estimator estimates the expected relative number of patients (cumulative incidence function [CIF]) of the event at hand. Treatment effects were to be derived in terms of the absolute differences between the treatment arm-specific estimators evaluated at day 7:

〖Effect〗_(Y;7)=CIF_Y^A (7)- CIF_Y^B (7)

where 〖CIF〗_Y^X (7) is the Aalen-Johansen estimator evaluated at day 7 for endpoint Y∈{Death, Early Response, Late Response} within treatment group X∈{A,B}. In order to test the hypotheses

H0: 〖Effect〗_(Y;7)=0=0 vs H1: 〖Effect〗_(Y;7)≠0

Two-sided confidence intervals (CIs) were to be constructed based on the approximate normality of the estimators (Beyersmann 2012). Statistical significance was to be concluded if the two-sided 95% CI did not cover 0.

Adjustment for relevant baseline covariates (age, sex, oxygenation index and intubation status) were to be realized by cause-specific Cox models. Subdistribution hazards regression modelling were to be applied in the presence of competing risks (Fine and Gray 1999) to explore the relative covariate effects in terms of the CIF of interest. Model assumptions were to be checked using graphical diagnostics.

All-cause mortality was to be analyzed as a censored time-to-event variable with Kaplan-Meier methods. The proportion of patients still alive at 28 days was to be derived based on the product limits estimator in each treatment arm. Adjustment for relevant baseline covariates (age, sex, oxygenation index, and intubation status) was to be realized by the Cox proportional hazard model.

The individual components of the composite time-to-event endpoints early and late response and ICU discharge were to be analyzed descriptively.

Laboratory endpoints as well as the Glasgow Outcome Scale were to be analyzed descriptively by time point and treatment arm.

10.1.3.2. Safety Analyses

The occurrence of AEs was to be compared between treatment arms. Treatment-emergent AEs (TEAEs) were to be analyzed according to the number and percentage of patients who had a

TEAE, as well as the number of TEAEs with the respective Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Additionally, the number and percentage of patients with TEAEs were to be further grouped by severity and causal relationship. The number and percentage of patients with SAEs and the number of SAEs were to be analyzed. Where AEs were grouped by severity or relationship, the maximum severity/relationship per patient and class of AE was to be considered.

10.1.3.3. Interim Analysis

An interim analysis was performed after the first 30 patients treated in Phase II reached at least day 15 of the study schedule to assess the clinical benefit of the treatment using the assessed clinical parameters.

10.2. Phase III

10.2.1. Sample Size Determination

A total of 180 patients (90 per arm) are planned to be randomized in Stage 1 and up to 180 patients (90 per arm) in Stage 2. For patients randomized in error (screening failures) and patients for whom consent is withdrawn within 48 hours after randomization, additional patients will be randomized. This results in 90% overall power to show efficacy in the final efficacy analysis. The power calculation is based on an overall 2.5% one-sided alpha and an assumed 30% 28-day mortality under Placebo and 15% 28-day mortality under IFX-1 treatment.

10.2.2. Analysis Sets

Full analysis set (FAS): The primary statistical analysis will be based on all randomized patients except patients randomized in error (reason for early termination documented as “Randomized by mistake” in the eCRF) who did not get IMP treatment.

Safety analysis set (SAF): Safety analyses will be based on all patients who received at least one infusion of IMP, and patients will be analyzed according to the treatment they actually received.

10.2.3. Statistical Analyses

The SAP will be developed and finalized before the study will be unblinded. The SAP will include the exact definition of endpoints and variables to be analyzed, extensive details on the statistical analysis methods to be used together with the structure of tables and figures to be included as end-of-text tables and figures as well as appended listings for the clinical study report. It will also describe procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and other endpoints.

Individual data will be listed. Data will be summarized using suitable descriptive statistics; depending on the structure of the data, summary statistics (e.g., number of observations, mean, standard deviation, minimum, median, maximum, lower quartile, upper quartile) or frequency tables may be used.

All data will be displayed by treatment arm if not specified otherwise.

10.2.3.1. Primary Efficacy Analysis

The primary analysis will be performed based on the FAS.

The primary efficacy variable is 28-day mortality (proportion of patients deceased until day 28). The primary statistical hypotheses to be tested are:

H_0: HR = 1

versus

H_1: HR > 1

where HR is the hazard ratio derived from the beta coefficient of the primary statistical analysis Cox regression model comparing the SOC + Placebo treatment arm (Arm B) with the SOC + IFX-1 treatment arm (Arm A).

A total of 180 patients are planned to be randomized to Arm A and Arm B using a 1:1 allocation ratio for the first stage. The interim analysis is performed after 180 patients, not counting patients being randomized in error, have been followed-up until day 28 (or died before). In case the interim analysis does not result in an early stop for futility, 180 additional patients are planned to be randomized in a ratio of 1:1 to Arm A and B. The planned maximum number of patients in the study is 360. Depending on the number of patients meeting criteria for additional randomization, more patients will be randomized but not more than 400.

The primary statistical analysis of IFX-1 + SOC compared to SOC alone will make use of a one-sided alpha level of 2.5% and will test for superiority (lower mortality among IFX-1 treated patients). The primary statistical analysis will be based on a Cox proportional hazards regression model with outcome 28-day all-cause mortality as a censored time-to-event variable and explanatory variables treatment arm (Arm B versus Arm A) and age. The primary statistical analysis will be based on all randomized patients except patients randomized in error (reason for early termination documented as “Randomized by mistake” in the eCRF) who did not get IMP treatment.. For the primary analysis, all-cause mortality will be censored at day 28 for subjects who died after day 28 or who have more than 28 days follow-up alive.

The z-statistic for the interim and final analysis will be calculated as the proportion of the beta coefficient for the treatment arm effect and its standard error from the Cox proportional hazards

regression model. The study will be stopped for futility if the z-statistic for the first stage is 0 or lower.

10.2.3.2. Secondary Efficacy Analyses

The secondary efficacy analyses will be performed based on the FAS.

The first secondary efficacy endpoint will only be addressed with statistical hypothesis tests if the primary endpoint is statistically significant using the full overall 2.5% one-sided alpha. If the first secondary endpoint is also statistically significant, the full 2.5% one-sided alpha will be passed to the 4 remaining secondary endpoints. Multiplicity in the secondary endpoints will be addressed with the fallback method. 60-day mortality will be analyzed similar to 28-day mortality and the other secondary endpoints will be evaluated using a logistic regression model with the explanatory variables randomized treatment arm (Arm B versus Arm A) and age for:

1. 60-day all-cause mortality
2. Proportion of patients with an improvement in the provided 8-point ordinal scale at day 15 (at least one score point lower than at randomization)
3. Proportion of patients with an improvement in the provided 8-point ordinal scale at day 28 (at least one score point lower than at randomization)
4. Proportion of patients developing acute kidney failure (eGFR < 15 mL/min/1.73m²) during ICU stay and at day 28
5. Proportion of patients free of any renal replacement therapy within 28 days upon randomization
6.

The ordering of the secondary endpoints 2 to 5 for hypothesis testing will be as in above mentioned list. The full 2.5% one-sided alpha for the fallback method will be attributed to the 4 secondary endpoints in the following way 2%, 0.2%, 0.2%, and 0.1%. If the preceding hypothesis test is not significant, subsequent tests will be performed at the aforementioned alpha level. If tests are significant, the alpha is added to the subsequent hypothesis test (e.g., if the primary hypothesis test is significant and secondary endpoints 1-4 are all significant, the fifth secondary endpoint will be tested at an alpha of 2.5%; if the fourth secondary endpoint is not significant, the fifth secondary endpoint will be tested at an alpha of 0.1%).

The primary endpoint as well as all secondary endpoints will also be evaluated as censored time to event variables by Kaplan-Meier type methods. Kaplan-Meier analyses will be performed comparing the two treatment arms overall and within the following stratifications:

- Stratification by site
- Stratification by country

- Stratification by sex
- Stratification by age
- Stratification by comorbidities
- Stratification by standard or care.

10.2.3.3. Other Efficacy Analyses

Time to First Extubation

Time to first extubation will be analyzed as a censored time to event variable. Withdrawing early from the study will lead to the patient being right-censored at the date of withdrawal provided that the reason is not an outcome of interest (extubation or death). In order to adequately account for competing outcomes as well as potential right-censoring due to varying follow-up times, the outcome will be non-parametrically analyzed using Aalen-Johansen-type estimation based on a competing risks model with two absorbing states (event 1: all-cause death; event 2: extubation). Adjustment for age will be realized by regression modeling accounting for competing risks.

Patients Alive and Free of Respiratory Failure

Patients achieving 8-point ordinal scale score 3 or below (patients alive and free of respiratory failure) at day 15 and day 28 are defined as alive and free of respiratory failure at the respective study day. The corresponding endpoint will be analyzed using logistic regression with explanatory variables age and treatment group.

Glasgow Outcome Scale

Glasgow Outcome Scale assessed at study day 60 will be analyzed via ordinal logistic regression with explanatory variables treatment arm (Arm B versus Arm A) and age.

Quality of Life

Quality of life will be assessed by EQ-5D at study day 60. The visual analogue scale as well as an index value based on the 5 health states (cross-walk index value using the United States value set) will be analyzed by an ANCOVA model with explanatory variables treatment arm (Arm B versus Arm A), age, and sex (male versus female).

10.2.3.4. Safety Analyses

Safety analyses will be performed based on the SAF.

The occurrence of TEAEs will be compared between treatment arms. TEAEs will be analyzed according to the number and percentage of patients who had a TEAE, as well as the number of TEAEs in total. Additionally, the number and percentage of patients with TEAEs will be further grouped by severity and causal relationship. The number and percentage of patients with serious

TEAEs and AESIs and the number of serious TEAEs and AESIs will be analyzed. Where TEAEs are grouped by severity or relationship, the maximum severity/relationship per patient and class of TEAE will be considered.

10.2.3.5. Interim Analysis

The interim analysis is performed after the first 180 patients, not counting patients being randomized in error, in Stage 1 have been followed-up until day 28 (or died before). The study will be stopped for futility if the z-statistic of the primary efficacy analysis is 0 or lower. If the study is not stopped for futility, another up to 180 patients will be randomized in Stage 2. Depending on the number of patients meeting criteria for additional randomization, more than 360 patients will be randomized but not more than a total of 400.

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12. APPENDICES

Appendix 1 Clinical Laboratory Tests

The protocol-required laboratory assessments are detailed in Table 3 for Phase II and in Table 4 for Phase III. Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 6.1 and Section 6.2 of the protocol. In general, blood samples for safety laboratory analysis should be obtained once a day during a routine sampling (preferable in the morning) prior to IMP administration. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 3 Protocol-Required Safety Laboratory Assessments: Phase II

Assessment	Parameters	
Hematology	Hemoglobin Hematocrit Platelet count Red blood cell count Red blood cells (MCV)	White blood cell count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Coagulation parameters	APTT PT	D-Dimer
Clinical chemistry [a]	ALT (SGPT) AST (SGOT) LDH Total bilirubin Creatinine Procalcitonin	Sodium Potassium Calcium Magnesium Glucose CRP
Urinalysis (Dipstick)	PH Glucose Leucocytes Protein Blood	
Other screening tests	Troponin ISerum or urine hCG pregnancy test (as needed in women of childbearing potential)	

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring are given in Section 9.5.3. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (35% direct bilirubin) or ALT ≥3 ULN and INR >1.5 (if INR is measured), may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE.

Table 4 Protocol-Required Safety Laboratory Assessments: Phase III

Assessment	Parameters
Screening/Randomization Only (as indicated in SoA Table 2)	
Urinalysis	PH Glucose Leucocytes Protein Blood
Other screening tests	Serum or urine human chorionic gonadotropin/hCG pregnancy test (in women of childbearing potential)
Screening/Randomization and Treatment (as indicated in SoA Table 2)	
Hematology	Hemoglobin Hematocrit Platelet count Red blood cell count Red blood cells (MCV) White blood cell count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Coagulation parameters	APTT PT D-Dimer
Clinical chemistry [a]	ALT (SGPT) AST (SGOT) LDH Total bilirubin CRP

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring are the same as in Phase II (listed in Section 9.5.3). All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (35% direct bilirubin) or ALT ≥3 ULN and international normalized ratio (INR) >1.5 (if INR is measured), may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE.

Investigators must document their review of each laboratory safety report.

Appendix 2 Regulatory and Ethical Considerations

I. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other relevant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

II. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

III. Informed Consent Process

Obtaining of informed consent is proposed to be deferred for the ICU patients in this study or by any other legally acceptable local procedure specific for patients treated in the ICU setting (see Section 6.3).

The ICF could contain a separate section or an additional ICF may be issued that addresses the use of remaining samples for optional exploratory research. The investigator or authorized designee will explain to each patient/legal representative the objectives of the exploratory research. Patients/legal representatives will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will not provide this separate signature.

IV. Data Protection

Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient and/or the legal representative/relative must be informed that patients' personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor will ensure that all safeguards are in place to minimize any eventual risk of breaches and complies otherwise with the requirements of European Union (EU) General Data Protection Regulation (GDPR [EU] 2016/679). The sponsor will regularly check all procedures relevant to the processing of personal data, as to ensure privacy by design and compliance with this regulation.

V. Publication Policy

The results of this study may be published or presented at scientific meetings. Individual publications are allowed only after publication of the entire study. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of

multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

In accordance with consistent editorial practice, the sponsor supports publication of multicenter studies in their entirety and not as individual center data unless as ancillary study/data.

All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record (e.g., on ClinicalTrials.gov).

VI. Dissemination of Clinical Study Information

The sponsor will provide the relevant study protocol information in a public database (e.g., ClinicalTrials.gov, https://clinicaltrials.gov/) before or at commencement of the study. The sponsor may also provide study information for inclusion in national registries according to local regulatory requirements.

If a potential patient contacts the sponsor regarding participation in the study, the investigator agrees that the sponsor may forward the study site and contact details to the patient. Based on the inclusion and exclusion criteria for the study, the investigator will assess the suitability of the patient for enrollment into the study.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record (e.g., on ClinicalTrials.gov).

VII. Data Quality Assurance

All patient data relating to the study will be recorded on the eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

It is the responsibility of the site to comply with the protocol-defined procedures and assessments. Details about the handling of protocol deviations will be included in a separate Protocol Deviation Plan.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing on-site or remote source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study, must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

VIII. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study.

IX. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further IMP development

Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluation, Follow-up, and Reporting

I. Definitions

Definition of an AE
An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of IMP, whether or not considered related to the IMP. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline. Laboratory tests are considered abnormal, if – Any criterion for an SAE is fulfilled – The abnormality causes the patient to discontinue from the study treatment – The abnormality causes the patient to interrupt the study treatment or a modification of dosing – The investigator judges that the abnormality is clinically significant and hence is to be reported as an (S)AE in the eCRF • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Signs, symptoms, and/or clinical sequelae resulting from disease progression will be reported as AE or SAE if they fulfil the definition of an AE or SAE. The terms ‘disease progression’, ‘progressive disease’, or similar, per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.
Events <u>NOT</u> Meeting the AE Definition
• The terms ‘progressive disease’ or ‘progression of disease’ per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Definition of an SAE

If an event is not an AE according to the above definition, then it cannot be an SAE even if serious conditions are met.

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

- Results in death

- Is life-threatening

Life-threatening in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

- Required inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent disability or incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect

- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the

patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Definition of an Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined (as per ICH Topic E2A) as all noxious and unintended responses to a medicinal product related to any dose which nature or severity is not consistent with the relevant source document, i.e., current IB. When reported as serious, the unexpected adverse reaction is defined as suspected unexpected serious adverse reaction. The safety vendor is responsible for notifying suspected unexpected serious adverse reactions to concerned regulatory bodies in accordance with local regulations.

II. Procedures for Recording, Evaluation, Follow-up and Reporting of an AE, including AESIs and SAEs

Recording of AEs, including AESIs and SAEs

- When an AE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE.
- The investigator will then record all relevant information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the patient's medical records to the safety vendor in lieu of completion of the respective sections of the eCRF.
- There may be instances when copies of medical records for certain cases are requested by the safety vendor. In this case, all patient identifiers, with the exception of the patient number, must be redacted on the copies of the medical records before submission to the safety vendor.

SAE Reporting to the Safety Vendor via the eCRF

- The safety vendor for this study is IQVIA Pharmacovigilance and is responsible for SAE processing and reporting.
- The primary mechanism for reporting an SAE to the safety vendor will be the eCRF.
- Investigators and other site personnel must report those SAEs that are outlined under Section 9.2 within 24 hours of becoming aware. The same applies for follow-up information on SAEs.

- A paper SAE reporting form needs to be completed by the investigator or other relevant site staff, signed by the investigator, and faxed to +353 1 809 9501 or QLS_IFX1@iqvia.com in case eCRF SAE reporting is not possible.

Assessment of Intensity for AEs, including AESIs and SAEs

The investigator will make an assessment of intensity for each AE reported during the study and assign it to 1 of the following categories (National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] v5.0):

- Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 (Moderate): minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*
- Grade 3 (Severe/medically relevant but not immediately life-threatening); hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- Grade 4 (Life-threatening): Life-threatening consequences; urgent intervention indicated
- Grade 5 (Death): Death related to AE

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Assessment of Causality of AEs, including AESIs and SAEs

- The investigator is obligated to assess the relationship between IMP and each occurrence of each AE.
- A ‘reasonable possibility‘ of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered, investigated, and reported.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the safety vendor. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the safety vendor.

- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs, including AESIs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or the safety vendor to elucidate the nature and/or causality of the AE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- In case of persisting SAEs, follow-up must continue until the AEs have resolved to grade ≤1 or baseline or are deemed irreversible by the investigator.
- If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the safety vendor with a copy of any post-mortem findings including histopathology, if any would become available.
- The investigator will submit any updated SAE data to the safety vendor within 24 hours of receipt of the information.

III. Special Considerations for Assessment of Adverse Events in an ICU Setting

Due to the severity of disease of the patient population entering this study, numerous problems, signs, and symptoms deviating from normal will be seen during the course of the study. These will not necessarily constitute a reportable AE unless they require significant intervention, lead to discontinuation of blinded study drug, or are considered to be of concern in the investigator's clinical judgement, i.e. classified as "clinically significant". Similarly, it is preferred to receive documentation of the underlying condition rather than the resulting sign (e.g., 'agitation' rather than 'self-extubation').

In clinical studies in intensive care, deviations, e.g., in laboratory values or temporary changes in arterial blood pressure, are to be expected frequently. Clinical judgement should be applied in determining which deviations should be reported as an AE in the sense of an "untoward medical occurrence" and which deviations should be considered usual and expected findings in this setting. To support the investigators, a separate list of non-reportable findings will be provided defining the parameters as well as the conditions when to report a deviation as an AE and when not.

It must be noted that clinically significant laboratory deterioration as assessed by the investigator must be documented in the respective eCRF section. However, it is preferred to document the condition or disease underlying the aberrant laboratory value (e.g., renal failure rather than hyperkalemia) rather than the laboratory value only.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant, and thus constitutes an AE.

Appendix 4 Contraceptive Guidance and Collections of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

3. Postmenopausal female:
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male Patients

Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the study and until 3 months after last dose of IFX-1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 5 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration [during the protocol-defined time frame].

Female Patients

Female patients of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception (from the day of study medication initiation throughout the study period and up to 3 months for IFX-1 after the last dose of study medication) consistently and correctly as described in Table 5. During the treatment period of the study conception is assumed to be precluded by the severe clinical conditions for included patients and applicability of sexual abstinence as a contraceptive method can be assessed by the investigator in case a patient confirmation cannot be gained.

Table 5 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User-Dependent [a] (failure rate of <1% per year when used consistently and correctly)
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: [b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User-Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation: [b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion

Vasectomized partner: A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies.
b Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 3 months after the last dose of IFX-1.

Pregnancy Testing

WOCBP should only be included after a negative serum or urine pregnancy test.

Collection of Pregnancy Information

Male Patients with Partners who Become Pregnant

The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive IFX-1.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients who Become Pregnant

The investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and

submitted to the sponsor within 24 hours of learning of a patient's pregnancy. The patient will be followed at least monthly to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the IMP by the investigator will be reported to the safety vendor as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating in the study will discontinue IMP.

Appendix 5 Treatment Modification Guidelines

Table 6 Dose Modification and Toxicity Management Guidelines for Infusion Reactions Associated with IFX-1

Grade	Treatment	Premedication at Subsequent Dosing
mild Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
moderate Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Patient may be premedicated 1.5 h (± 30 minutes) prior to infusion of IMP with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
severe Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. ** In cases of anaphylaxis, epinephrine should be used immediately.	No subsequent dosing

life-threatening: Life-threatening; pressor or ventilator support indicated	Patient is **permanently discontinued** from further **study drug treatment**.	

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

Appendix 6 Conversion Tables for PaO_2 / FiO_2 Ratio

The following conversion tables should be used if a blood gas analysis is not available.

Estimating PaO_2 from a measured SO_2

SO_2	Calculated PaO_2 (mmHg)	SO_2	Calculated PaO_2 (mmHg)	SO_2	Calculated PaO_2 (mmHg)
80	44	87	53	94	73
81	45	88	55	95	79
82	46	89	57	96	86
83	47	90	60	97	96
84	49	91	62	98	112
85	50	92	65	99	145
86	52	93	69		

Estimating FiO_2 with known O_2 Application Flow

Method	O_2-Flow (l/min)	Estimated FiO_2 (%)
Nasal O_2 Tube Nasal Prong	1 2 3 4 5 6	24 28 32 36 40 44
Nasopharyngeal Catheter	4 5 6	40 50 60
Oxygen Mask	5 6–7 7–8	40 50 60
Oxygen Mask with Reservoir	6 7 8 9 10	60 70 80 90 95

Appendix 7 Ordinal Scale

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Appendix 8 Glasgow Outcome Scale

The **Glasgow Outcome Scale** is a global scale for functional outcome that rates patient status into one of five categories:

Rate	Category
1	Death
2	Persistent vegetative state
3	Severe disability (conscious but disabled)
4	Moderate disability (disabled but independent)
5	Good recovery

Appendix 9 EQ-5D Health Questionnaire

The **EQ-5D** is a widely used multi attribute utility instrument for measuring health-related quality of life.

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

SELF-CARE

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

PAIN / DISCOMFORT

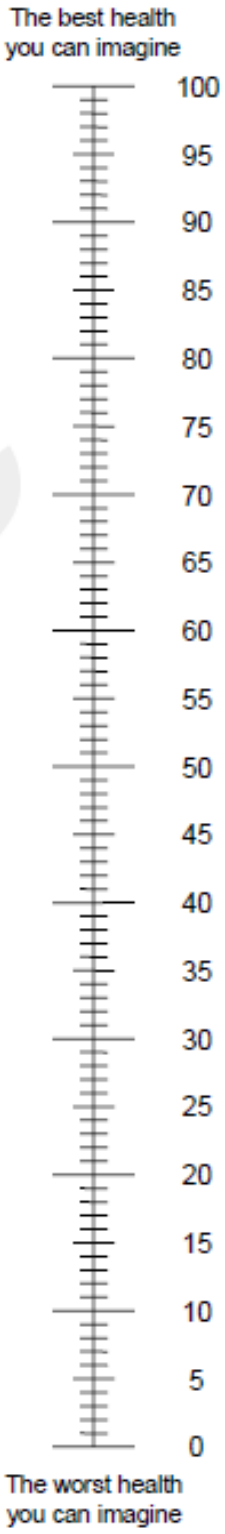
I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 10 New York Heart Association (NYHA) Classification

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath)
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Appendix 11 Child-Pugh Classification

Category	Hepatic Function	Score
Child-Pugh A	Good	5 to 6 points
Child-Pugh B	Moderately impaired	7 to 9 points
Child-Pugh C	Advanced hepatic dysfunction	10 to 15 points

	1 point	2 points	3 points
Encephalopathy:	None	Grade 1 and 2	Grade 3 and 4
Ascites:	None	Slight	Moderate
Bilirubin:	< 2 mg/mL	2 to 3 mg/mL	> 3 mg/mL
Albumin:	> 3.5mg/mL	2.8 to 3.5mg/mL	< 2.8mg/mL
Prothrombin Time: OR INR:	< 4 sec < 1.7	4 to 6 sec 1.7 to 2.2	> 6 sec > 2.2

Appendix 12 Special Considerations for Assessment of Prior and Concomitant Medications

A complete record of all prior and concomitant drugs (but excluding nutritional and volume therapy, electrolyte support, vitamins, NSAIDs, and supportive therapies such as artificial tears, ointments, stool softeners/laxatives, etc.) will be maintained in the eCRF for each participant, beginning 7 days before randomization and continuing until up to 30 days after the last dose of study treatment.

In addition, a complete record of all steroid and antibiotic therapy and any therapy (drugs, specific treatments, etc.) associated with or used in the assessment or treatment of an adverse event will be documented for the duration of the study.

The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, and indication.

All medications administered within 7 days before randomization should be recorded with generic name, route of administration, start date, stop date, and indication.

Appendix 13 Protocol Version History

VERSION 4.0: 12 MAY 2021

This protocol version is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU.

Overall Rationale for Version 4.0

Following Scientific Advice recommendations of the USA Federal Drug Administration and the European Medical Agency, the statistical 'stop for efficacy' criterion for the interim analysis has been removed, including adaptation of the power calculation, the randomization of additional patients clarified, and the order of secondary endpoints adapted.

Corresponding updates have been implemented in Protocol Version 4.0 for Phase III part of the study as described in Table 7 below.

Table 7 Protocol Version History: Updates to Version 4.0, Phase III

Section(s)	Description of Change	Brief Rationale
	Overall	Separation of protocol sections into subsections for Phase II and Phase III has been maintained, as study is designed as a combined Phase II/III study. Amended topics refer only to study design elements applicable to Phase III part of the study.
1 Synopsis,	Number of sites have been increased from 45 sites to 60 sites.	Given the still unpredictable epidemiology of COVID-19, additional sites will improve the ability to enroll the study in a timely manner.
1 Synopsis, 4.2.2.2, 5.1, 5.2, 10.2.1, 10.2.3.1, 10.2.3.2, 10.2.3.3, 10.2.3.5	Statistical 'stop for efficacy' criterion for the interim analysis has been removed, power calculation adapted, randomization of additional patients clarified, '60-day mortality' endpoint upgraded to the first secondary endpoint, and the order of the secondary endpoints adapted. Addition of an exploratory endpoint.	Adaptations performed to eliminate statistical concerns of regulatory authorities about the early stop for efficacy at interim analysis and to clarify final analysis.

Additional major updates made in Protocol Version 2.0 that were retrospectively applied to Phase II mainly include text that was simplified or adapted to an ICU setting, as described in the table below.

Table 8 Protocol Version History: Major Updates to Phase II

Section(s)	Description of Change	Brief Rationale
	Overall	Where applicable, protocol sections were separated into subsections for Phase II and Phase III.

Section(s)	Description of Change	Brief Rationale
		Because Phase II is now completed, all information relevant only to Phase II of the study has been changed to past tense and font color changed to grey. "Subject(s)" changed to "Patient(s)" throughout to reflect the COVID-19 diseased population, and not healthy subjects, in the trial.
5.5.1.3	Clarification made	Removed "In such a case the EOS visit information will be added to the EOT visit information.", as this language was unclear.
5.5.1.4	Text on patients lost to follow-up updated	Text adapted to an ICU setting
6.4	Revised definition of screening failures	Text adapted to an ICU setting
6.5	Removed dietary requirements	Text adapted to an ICU setting
7.2, 7.3, 9.2.1, 9.6, Appendix 5	"Infusion-related reactions" was changed to "infusion reactions"	"Infusion reactions" is more a more accurate description of these events.
7.2.4	Removed "disease progression"	Text adapted to an ICU setting
7.3	Removed "in the treatment facility"	Text adapted to an ICU setting
7.4	Requirements for recording of prior and concomitant medications were revised	Requirements were simplified and adapted to an ICU setting
9.1	Text on frequency of collection and reporting revised	AESIs were included in the specified AEs to be reported until 30 days following the last IFX-1 administration. SAEs was moved to the first bullet; bullets 1 and 2 combined since they follow the same timelines
9.1.1, 9.1.1.1, 9.1.2	Headings renamed and text updated accordingly	Removed visit names that were used only in Phase II, to make the text applicable to Phase III as well.
9.1.1.1, 9.2.1	"Death" was revised to "Events with fatal outcome"	Death is not an SAE, but the outcome of an SAE.
9.2.2	"Not Related" was changed to "Unrelated"	Harmonization of terminology