

Novartis Research and Development

DFV890

Clinical Trial Protocol CDFV890D12201 / NCT04382053

Phase 2, randomized, controlled, open label multi-center study to assess efficacy and safety of DFV890 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function

Document type: Amended Clinical Trial Protocol

EUDRACT number: 2020-001870-32

Version number: 01 (Clean)

Clinical Trial Phase: II

Release date: 22-JUN-2020

Property of Novartis

Confidential

May not be used, divulged, published, or otherwise disclosed
without the consent of Novartis

Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020

Table of contents

Table of contents	2
List of tables	6
List of figures	6
List of abbreviations	7
Glossary of terms.....	11
Commercially Confidential Information	
Protocol summary.....	21
1 Introduction	25
1.1 Background.....	25
1.1.1 Innate immunity during viral infection	25
1.1.2 Reduced activation of NLRP3 inflammasome in asymptomatic host species	26
1.1.3 Excessive inflammasome activation in the elderly	26
1.1.4 Coronavirus activation of the inflammasome may promote lung pathology.....	27
1.1.5 Inflammasome activation by mechanical ventilation and ARDS	27
1.1.6 Translational evidence that the NLRP3 inflammasome is activated in patients with coronavirus lung pathology	27
1.1.7 Inflammasome in acute organ injury and sepsis	28
1.1.8 Summary	28
1.2 DFV890	29
1.3 Purpose	32
2 Objectives and endpoints.....	32
2.1 Primary estimands	33
2.2 Secondary estimands	34
3 Study design	34
4 Rationale.....	35
4.1 Rationale for study design	35
4.2 Rationale for participant numbers and endpoint.....	36
4.3 Rationale for choice of background therapy.....	37
4.4 Rationale for dose/regimen and duration of treatment	37
4.5 Rationale for choice of control drugs (comparator/placebo) or combination drugs	39
4.6 Purpose and timing of interim analyses/design adaptations.....	39
4.7 Risks and benefits	39
4.7.1 Potential benefits and risks to study participants.....	39

4.7.2	Potential risks to participants	39
4.7.3	Overall risk benefit.....	41
4.8	Blood sample volume	42
5	Study Population	42
5.1	Inclusion criteria	42
5.2	Exclusion criteria.....	43
6	Treatment.....	44
6.1	Study treatment.....	44
6.1.1	Investigational and control drugs.....	44
6.1.2	Additional study treatments	45
6.1.3	Treatment arms/group	45
6.2	Other treatment(s).....	45
6.2.1	Concomitant therapy	45
6.3	Participant numbering, treatment assignment, randomization	48
6.3.1	Participant numbering	48
6.3.2	Treatment assignment, randomization	48
6.4	Treatment blinding.....	49
6.5	Dose escalation and dose modification.....	49
6.6	Additional treatment guidance.....	49
6.6.1	Treatment compliance.....	49
6.6.2	Recommended treatment of adverse events.....	50
6.6.3	Emergency breaking of assigned treatment code.....	50
6.7	Preparation and dispensation	50
6.7.1	Handling of study treatment and additional treatment.....	50
6.7.2	Instruction for prescribing and taking study treatment	51
7	Informed consent procedures	51
8	Visit schedule and assessments	52
8.1	Screening	56
8.1.1	Information to be collected on screening failures	56
8.2	Participant demographics/other baseline characteristics	56
8.2.1	Demographic information	56
8.2.2	Prior and concomitant medications.....	57
8.3	Efficacy.....	57
8.3.1	APACHE II severity of disease score	57
8.3.2	Clinical status (9-point ordinal scale)	57
8.3.3	CRP	57

8.3.4	Appropriateness of efficacy assessments	57
8.4	Safety	57
8.4.1	Laboratory evaluations	58
8.4.2	Special clinical laboratory evaluations.....	58
8.4.3	Physical examination	58
8.4.4	Vital signs	59
8.4.5	Height and weight	59
8.4.6	Electrocardiogram (ECG)	59
8.4.7	Pregnancy and assessments of fertility	60
8.4.8	Chest X-ray	60
8.4.9	Appropriateness of safety measurements.....	60
8.5	Additional assessments	60
8.5.1	SARS-CoV-2 virus testing.....	60

Commercially Confidential Information

9	Study discontinuation and completion	63
9.1	Discontinuation and completion	63
9.1.1	Study treatment discontinuation and study discontinuation	63
9.1.2	Withdrawal of informed consent.....	64
9.1.3	Lost to follow-up.....	65
9.1.4	Study stopping rules.....	65
9.1.5	Early study termination by the sponsor.....	65
9.2	Study completion and post-study treatment	65
10	Safety monitoring and reporting.....	66
10.1	Definition of adverse events and reporting requirements.....	66
10.1.1	Adverse events	66
10.1.2	Serious adverse events	67
10.1.3	SAE reporting	68
10.1.4	Pregnancy reporting	69
10.1.5	Reporting of study treatment errors including misuse/abuse.....	69
10.2	Additional Safety Monitoring.....	70
10.2.1	Liver safety monitoring.....	70
10.2.2	Data Monitoring Committee	71

11	Data Collection and Database management	71
11.1	Data collection	71
11.2	Database management and quality control	71
11.3	Site monitoring	72
12	Data analysis and statistical methods	73
12.1	Analysis sets	73
12.2	Participant demographics and other baseline characteristics	73
12.3	Treatments	73
12.4	Analysis of the primary endpoint(s)/estimand(s)	74
12.4.1	Definition of primary endpoint(s)/estimand(s)	74
12.4.2	Statistical model, hypothesis, and method of analysis	74
12.4.3	Handling of remaining intercurrent events of primary estimand	74
12.4.4	Handling of missing values not related to intercurrent event	74
12.4.5	Sensitivity analyses for primary endpoint/estimand	74
12.4.6	Supplementary analysis	74
12.4.7	Supportive analyses	74
12.5	Analysis of secondary endpoints/estimands	74
12.5.1	Efficacy and/or Pharmacodynamic endpoint(s)	74
12.5.2	Safety endpoints	75
	Commercially Confidential Information	
12.6	Analysis of exploratory endpoints	76
	Commercially Confidential Information	
12.8	Interim analyses	77
12.9	Sample size calculation	77
12.9.1	Primary endpoint(s)	77
12.9.2	Secondary endpoint(s)	77
13	Ethical considerations and administrative procedures	77
13.1	Regulatory and ethical compliance	77
13.2	Responsibilities of the investigator and IRB/IEC	77
13.3	Publication of study protocol and results	78
13.4	Quality Control and Quality Assurance	78
14	Protocol adherence	78
14.1	Protocol amendments	78
15	References	80
16	Appendices	85

16.1	Appendix 1: 9-point ordinal scale determination	85
16.2	Appendix 2: Liver event and laboratory trigger definitions and follow-up requirements	86
16.3	Appendix 3: Severity of disease classification systems	88
16.4	Appendix 4: Severity of hepatic impairment (Child-Pugh).....	90

List of tables

Table 2-1	Objectives and related endpoints	32
	Commercially Confidential Information	
Table 6-1	Investigational and control drug.....	45
Table 6-2	Concomitant medications to be used with caution.....	48
Table 6-3	Dose and treatment schedule.....	51
Table 8-1	Assessment schedule.....	53
Table 8-2	Clinical laboratory tests (locally).....	58
Table 10-1	Guidance for capturing the investigational treatment errors including misuse/abuse	70
Table 16-1	9-point ordinal scale.....	85
Table 16-2	Liver event and laboratory trigger definitions	86
Table 16-3	Follow up requirements for liver laboratory triggers.....	87
Table 16-4	APACHE II	88
	Commercially Confidential Information	
Table 16-7	Child-Pugh scores and classification	90

List of figures

Figure 1-1	Working model for ORF3a-induced activation of the NLRP3 inflammasome.....	29
Figure 3-1	Study design.....	34

List of abbreviations

%	Percentage
°C	Degrees Celsius
°F	Degrees Fahrenheit
AE(s)	Adverse event(s)
AIDS	Acquired immune deficiency syndrome
AKI	Acute kidney injury
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APACHE II	Acute Physiology and Chronic Health Evaluation II
APTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
Commercially Confidential Information	
BiPAP	Bilevel positive airway pressure
BMI	Body mass index
NT-proBNP	N-Terminal ProB-type Natriuretic Peptide
BP	Blood Pressure
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CAPS	Cryopyrin-associated periodic syndromes
Center No.	Center Number
CIs	Confidence Interval(s)
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cm	Centimeters
Cmax	Maximum serum concentration
CMO&PS	Novartis Chief Medical Office and Patient Safety
CO	Country Organisation
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
CT scan	Computed tomography scan
CTC	Common Toxicity Criteria
CV	Coefficient of variation
CVD	Cardiovascular diseases
CXR	Chest X-ray

CYP	Cytochrome P450
CYP2C9	Cytochrome P450 2C9
CYP3A	Cytochrome P450, family 3, subfamily A
CYP3A4	Cytochrome P450 3A4
DBP	Diastolic blood pressure
DDE	Direct Data Entry
dL	Deciliter
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
eATP	Extracellular adenosine triphosphate
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRFs	Electronic Case Report Forms
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EU	European Union
FAS	Full Analysis Set
FIH	First-in-human
FiO ₂	Fraction of inspired oxygen
g	Gram
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl-transferase
GLP	Good Laboratory Practice
h	Hours
HA	Health Authority
HDL	High-density lipoprotein
HV(s)	Healthy volunteer(s)
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
IC50	half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IEC	Independent Ethics Committee
IFN- γ	Interferon-gamma
IL	Interleukin

IMMs	Inflammatory monocyte-macrophages
IN	Investigator Notification
INR	International normalized ratio
IP-10/CXCL10	Interferon gamma-induced protein 10 / C-X-C motif chemokine 10
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
Commercially Confidential Information	
LPS	Lipopolysaccharide
m	Meter
m ²	Square meter
MABEL	Minimum anticipated biological effect level
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
mEq	Milliequivalents
mg	Milligram
min	Minute
mL	Milliliter
mm ³	Cubic millimeter
mmHg	Millimeter of mercury
MR scan	Magnetic resonance scan
NASH	Non-alcoholic steatohepatitis
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
ng	Nanogram
NK cells	Natural killer cells
nM	Nanomolar
NOAEL	No-observed-adverse-effect level
PA	Posteroanterior
PaO ₂	Partial pressure of oxygen
Participant No.	Participant Number
PBMCs	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PEEP	Positive end-expiratory pressures
pH	Power of hydrogen
Commercially Confidential Information	
PoC	Proof of Concept

PoM	Proof of Mechanism
PR	Pulse rate
PRR	Pattern recognition receptors
PT	Prothrombin time
PT/INR	Prothrombin time/international normalized ratio
PTT	Partial thromboplastin time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RRT	Renal replacement therapy
SAE(s)	Serious Adverse Event(s)
Commercially Confidential Information	
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SD	Standard deviation
SMQ	Standardized MedDRA Query
SoC	Standard of care
Commercially Confidential Information	
SOP(s)	Standard Operating Procedure(s)
SpO ₂	Peripheral oxygen saturation
SUSARs	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TLR	Toll-like receptor
TNF- α	Tumor necrosis factor alpha
Ub	Ubiquitin
ULN	Upper limit of normal
Commercially Confidential Information	
US	United States of America
WHO	World Health Organization
Commercially Confidential Information	
μ g	Microgram

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and eCRFs into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)

Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing

	the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Victim drug	The drug that is affected by the drug-drug interaction
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Protocol summary

Protocol number	CDFV890D12201
Full Title	Phase 2, randomized, controlled, open label multi-center study to assess efficacy and safety of DFV890 for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients with coronavirus disease 2019 (COVID-19) pneumonia and impaired respiratory function
Brief title	Study of efficacy and safety of DFV890 in patients with COVID-19 pneumonia
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the efficacy and safety of DFV890 in addition to current standard of care (SoC) compared with SoC alone in controlling the inflammatory syndrome and resultant acute respiratory distress syndrome (ARDS) in hospitalized patients presenting with COVID-19 pneumonia and impaired respiratory function
Primary Objective(s)	The primary objective of the study is to evaluate the effect of DFV890 in addition to SoC, compared with SoC alone, on the Acute Physiology and Chronic Health Evaluation II (APACHE II) score
Secondary Objectives	The secondary objectives of this study are: <ul style="list-style-type: none"> • To evaluate the effect of DFV890 in addition to SoC, compared with SoC alone, on inflammatory status • To evaluate the effect of DFV890 in addition to SoC, compared with SoC alone, on clinical status • To evaluate the safety of DFV890 in addition to SoC, compared with SoC alone
Study design	<p>This is a Phase 2, randomized, controlled, open label multi-center study to assess the efficacy and safety of DFV890 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function.</p> <p>The study consists of four parts:</p> <p>Screening / Baseline visit (Day -1 to 1): lasts up to a maximum of 24 hours and comprises a screening / baseline assessment. This visit will be used to confirm that the study inclusion and exclusion criteria are met and serves as baseline assessment prior to randomization.</p> <p>Treatment period (Day 1-15): Participants in the investigational treatment arm will receive DFV890 CCI . orally or via a nasogastric feeding tube administered for a total of 14 days CCI in addition to SoC. Study drug will be supplied in tablet form which can be crushed, allowing for both oral and nasogastric administration. Participants in the control arm will receive SoC alone.</p> <p>Participants will be randomized as soon as possible, but within a maximum of 24 hours after screening in a 1:1 ratio to receive either DFV890 in addition to SoC or SoC alone.</p>

	<p>Study assessments will be conducted every 2 days for hospitalized participants.</p> <p>The End of Treatment (EOT) visit will take place on Day 15. If participants are discharged from the hospital prior to Day 15, assessments on the day of discharge should be performed according to the schedule listed under Day 15; participants will continue to take the investigational treatment at home to complete the 14-day treatment period and the participants should return to the site for the Day 15/EOT assessment (all other visits between discharge and Day 15 can be omitted). If a hospital visit is not possible at Day 15, then home nursing services may be used to support this last visit where these are available in accordance with local guidelines and should include all possible assessments (e.g., oxygen saturation with portable monitors).</p> <p>Follow-up (Day 16-29): After completion of the 14 day- treatment period, participants will be observed until Day 29 or discharged from hospital, whichever is sooner. Study assessments to be conducted every 2 days for hospitalized participants.</p> <p>If participants are discharged from hospital prior to Day 29, a study visit conducted by telephone will occur on Day 29 (all other visits between discharge and Day 29 can be omitted).</p> <p>30-day safety follow-up assessment (Day 45): A follow-up visit for safety will be conducted by telephone.</p>
<p>Study population</p>	<p>Approximately 120 male and female patients between 18 and 80 years of age, inclusive.</p> <p>The study population includes adult male and female SARS-CoV-2 infected patients who are hospitalized and diagnosed with COVID-19 pneumonia and impaired respiratory function.</p>
<p>Key Inclusion criteria</p>	<ul style="list-style-type: none"> • Male and female patients aged 18-80 years inclusive at screening • Clinically diagnosed with the SARS-CoV-2 virus by polymerase chain reaction (PCR) or by other approved diagnostic methodology within 7 days prior to randomization • Hospitalized with COVID-19-induced pneumonia evidenced by chest X-ray, computed tomography scan (CT scan) or magnetic resonance scan (MR scan), taken within 5 days prior to randomization (within 24 hours in patients in the Netherlands) • Impaired respiratory function, defined as peripheral oxygen saturation (SpO₂) ≤93% on room air or partial pressure of oxygen (PaO₂) / fraction of inspired oxygen (FiO₂) <300 millimeter of mercury (mmHg) at screening. For cities located at altitudes greater than 2500 m above sea level, these will be substituted with SpO₂ <90% and PaO₂/FiO₂ <250 mmHg. • APACHE II score of ≥10 at screening • C-reactive protein (CRP) ≥20 mg/L and/or ferritin level ≥600 µg/L at screening • Body mass index of ≥18 to <40kg/m² at screening
<p>Key Exclusion criteria</p>	<ul style="list-style-type: none"> • Suspected active or chronic bacterial (including <i>Mycobacterium tuberculosis</i>), fungal, viral, or other infection (besides SARS-CoV-2) • In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatment • Intubated prior to randomization

	<ul style="list-style-type: none"> • Previous treatment with anti-rejection and immunomodulatory drugs within the past 2 weeks, or within the past 30 days or 5 half-lives (whichever is the longer) for immunomodulatory therapeutic antibodies or prohibited drugs (see Section 6.2.1.2), with the exception of hydroxychloroquine, chloroquine or corticosteroids: <ul style="list-style-type: none"> • For COVID-19 infection, ongoing corticosteroid treatment is permitted at doses as per local SoC • For non-COVID-19 disorders, ongoing corticosteroid treatment is permitted at doses up to and including prednisolone 10 mg daily or equivalent (see Section 6.2.1) • In patients in the Netherlands only, the use of hydroxychloroquine and/or chloroquine in the past 2 weeks are exclusionary • Serum alanine transaminase (ALT) or aspartate transaminase (AST) >5 times upper limit of normal detected within 24 hours at screening or at baseline (according to local laboratory reference ranges) or other evidence of severe hepatic impairment (Child-Pugh Class C, see Appendix 4) • Absolute peripheral blood neutrophil count of $\leq 1000/\text{mm}^3$ • Estimated GFR (eGFR) $\leq 30 \text{ mL}/\text{min}/1.73\text{m}^2$ (based on CKD-EPI formula) • Patients currently being treated with drugs known to be strong or moderate inducers of isoenzyme CYP2C9 and/or strong inhibitors of CYP2C9 and/or strong inducers of cytochrome P450, family 3, subfamily A (CYP3A) (see list of prohibited drugs: Section 6.2.1.2) and the treatment cannot be discontinued or switched to a different medication prior to starting study treatment • Patients with innate or acquired immunodeficiencies • Patients who have undergone solid organ or stem cell transplantation
<p>Study treatment</p>	<ul style="list-style-type: none"> • DFV890 CCI in addition to Standard of Care (SoC) • Standard of Care
<p>Treatment of interest</p>	<p>The randomized treatment (the investigational treatment DFV890 in addition to SoC or control treatment of SoC alone)</p>
<p>Efficacy assessments</p>	<ul style="list-style-type: none"> • APACHE II severity of disease score on Day 15 or on day of discharge (whichever is earlier) with worst case imputation for death • 9-point ordinal scale (Appendix 1): <ul style="list-style-type: none"> • Survival without the need for invasive mechanical ventilation at Days 15 and 29 • At least one level improvement in clinical status at Days 15 and 29 • Clinical status over time • Serum CRP levels • Number of participants with Adverse Event (AE), serious adverse events (SAE), clinically significant changes in laboratory measures, and vital signs
<p>Pharmacodynamic assessments</p>	<p>The pharmacodynamic objective for this study is to characterize the pharmacodynamic effects of DFV890 in patients with COVID-19 pneumonia via longitudinal measures of a number of analytes relative to baseline including the following:</p> <ul style="list-style-type: none"> • CRP, Commercially Confidential Information

<p>Commercially Confidential Information</p>	<p>Commercially Confidential Information</p>
<p>Key safety assessments</p>	<ul style="list-style-type: none"> • Incidence and severity of adverse events • Clinically significant changes in laboratory measures • Vital signs, electrocardiogram (ECG), Height and weight • Physical examination • Chest X-ray (CXR), CT or MR scan
<p>Other assessments</p>	<p>SARS-CoV-2 virus to be measured within 7 days prior to randomization</p> <p>Commercially Confidential Information</p>
<p>Data analysis</p>	<p>The primary endpoint will be evaluated by an analysis of covariance model including treatment group and the three stratification factors (age, anti-viral therapy, and presence of ≥ 1 comorbidities) as factors and baseline APACHE-II score as a covariate.</p> <p>For efficacy and pharmacodynamics endpoints, descriptive statistics (mean, standard deviation, median, minimum and maximum) will be provided for variables that are of the numeric or continuous type, while frequency distributions (with number and percent) will be provided for categorical variables.</p> <p>All listings and tables will be presented by treatment group.</p>
<p>Key words</p>	<p>COVID-19 pneumonia, SARS-CoV-2, APACHE II, DFV890, inflammasome</p>

1 Introduction

1.1 Background

As of 22-Apr-2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been confirmed in over 2.5 million people worldwide, with over 179,000 deaths to date due to coronavirus disease 2019 (COVID-19). The mortality rate of approximately 4-5% is significantly higher than that seen with seasonal influenza (less than 1%) and between 5-10% of COVID-19 patients develop lung injury, respiratory distress progressing to acute respiratory distress syndrome (ARDS) requiring prolonged ventilator support over weeks that results in intensive care units, hospitals and health care systems becoming overwhelmed.

ARDS is characterized by pro-inflammatory cytokine release, inflammatory cellular infiltrate and cell death resulting in severe pulmonary damage and the development of respiratory failure that requires mechanical ventilation with high positive end-expiratory pressures (PEEP) to maintain life. In patients with a prior history of hypertension, diabetes and cardiovascular disease, poor outcomes have been reported that may be as result of poor underlying cardiac reserve meaning that patients develop cardiac failure in response to ventilation, with pulmonary edema further exacerbating respiratory failure ([Zhou et al 2020a](#)).

Targeted treatment of the underlying hyper-inflammatory syndrome that occurs after initial SARS-CoV-2 infection in COVID-19 patients with respiratory failure has the potential to reduce the requirements for mechanical ventilation, the duration of mechanical ventilation and to improve the outcome for patients while also significantly reducing the demand on health care systems.

1.1.1 Innate immunity during viral infection

The innate immune system is the first line of defense against pathogens, including viruses. Pattern recognition receptors (PRR) are part of this system and are sensors for microbial structures. To safeguard the immune response, viruses can be sensed by many partially redundant, but also distinct classes of innate immune receptors, such as the nucleic-acid sensors, MDA-5 and RIG-I or members of inflammasome and Toll-like receptor (TLR) families. These sensors initiate a protective response that begins with the production of pro-inflammatory cytokines, such as type I interferons that restrict viral replication. In a subsequent wave of the host reaction to viruses, danger signals are released as tissues are damaged and cells are killed by the virus. The recognition of these danger signals by innate immune signaling receptors trigger further inflammatory responses ([Horvath et al 2011](#), [Franchi et al 2014](#)). A key sensor for danger signals released from dying cells is the NLRP3 inflammasome, which, upon activation, leads to the production and release of active IL-1 β and IL-18.

At low levels during initial stages of the disease, these cytokines amplify the innate immune response against viruses ([Tate et al 2016](#)) and promote the development of adaptive immune responses against the virus, providing long-term protection and reducing the risk of re-infection ([Ichinohe et al 2009](#)). However, when tissue damage from the virus or immune response is extensive, NLRP3 activation and the subsequent IL-1 β and IL-18 production can be excessive and beyond what is required to support an adaptive response, contributing to morbidity and mortality.

The concerted actions of the inflammasome will lead to exacerbated edema by direct activation of endothelial cells, increased tissue damage through neutrophil reactive species, and excessive type II interferon through IL-18 on T cells and natural killer cells (NK cells), and elicit or exacerbate other broad pro-inflammatory pathways, including IL-6, IL-17 and tumor necrosis factor alpha (TNF- α) (McAuley et al 2013, Ren et al 2017). Consistent with NLRP3 playing an underlying role in pulmonary pathology during viral infection, it has been shown in mice infected with influenza that inhibition of the NLRP3 inflammasome in the symptomatic phase of the infection reduces systemic inflammation as well as lung pathology without impairing viral clearance (Tate et al 2016, Coates et al 2017, Jia et al 2018).

Particularly, IL-18 is already constitutively expressed in the airway epithelium and parenchyma of human bronchial biopsies and its expression is largely further increased under inflammatory conditions such as in pulmonary sarcoidosis (Cameron et al 1999). IL-18 may not only activate Type 1 and Type 2 helper T cells and cytotoxic T cells, but has been reported to promote NK cell-mediated tissue damage. This was shown in the context of fulminant hepatitis A viral infection, in which inherited IL-18BP deficiency (the natural scavenger of bioactive IL-18) resulted in excessive NK cell activation by IL-18 and lead to the uncontrolled killing of human hepatocytes (Belkaya et al 2019). Together, IL-1 β and IL-18 can trigger innate and adaptive immune responses at the same time leading to exacerbated inflammation (Vanden Berghe et al 2014).

1.1.2 Reduced activation of NLRP3 inflammasome in asymptomatic host species

Bats are a reservoir of rapidly reproducing and highly transmissible viruses such as coronavirus. Indeed, the bat is the most likely source of origin of SARS-CoV-2, the causative virus of COVID-19 (Zhou et al 2020b). One notable feature of the bat immune system is that they are asymptomatic while carrying coronaviruses. The presumed reason why bats are asymptomatic is that, compared to other animals, viruses in bats do not induce a robust host inflammatory response, which in turn prevents the symptoms and pathology caused by tissue damage that occur when high levels of inflammation are generated. Recent findings indicate that NLRP3, but not other pro-inflammatory pathways such as NF- κ B, is 10-30 -fold less active in bats than in human cells. Importantly, coronavirus replication in bat and human peripheral blood mononuclear cells (PBMCs), and in PBMCs in which NLRP3 activity is inhibited, is comparable, confirming that NLRP3 does not play a role in controlling viral replication (Ahn et al 2019). This data suggests that NLRP3 inhibition may reduce the excessive inflammatory response responsible for the lung tissue damage that occurs in patients with COVID-19 without compromising antiviral immunity

1.1.3 Excessive inflammasome activation in the elderly

It is well documented that aging is clinically associated with an increase in levels of pro-inflammatory cytokines (e.g., IL-18, IL-6, IL-1Ra) (Ferrucci et al 2005). In mice, the pathway that mediates this chronic pro-inflammatory state is NLRP3-dependent (Youm et al 2013). Remarkably, NLRP3 activity in alveolar macrophages is greater in old mice compared to young mice, and this leads to an increased level of inflammation and fibrosis in older mice compared to younger mice (Stout-Delgado et al 2016). The increased NLRP3 activity in the elderly may

partly explain why the risk of severe pneumonia and death following infection with SARS-CoV-2 is positively associated with the age of patients.

1.1.4 Coronavirus activation of the inflammasome may promote lung pathology

Coronaviruses have been extensively studied in previous epidemic outbreaks. Even if the genomic information or structure of the current SARS-CoV-2 virus is not identical, the pathogenic mechanisms especially in severe cases seem to resemble very well previous viruses like SARS-CoV-1. Coronaviruses express transmembrane pore-forming proteins (Envelope (E) and Open reading frame (ORF) 3a, ORF8b) that alter ion conductance (Figure 1-1), eventually promoting K⁺ efflux, which in turn activates NLRP3 (ORF3a (Yue et al 2018, Chen et al 2019, Siu et al 2019); E (Nieto-Torres et al 2015); ORF8b (Shi et al 2019)). Consistent with the pathogenic role of NLRP3 in coronavirus-induced lung pathology, mice infected with viruses that express a form of protein E that can sustain viral replication, but that is not able to induce NLRP3 activation, fail to produce IL-1 β and do not develop pneumonia (Nieto-Torres et al 2014). In addition, factors generated during lung damage, such as extracellular adenosine triphosphate (eATP) (Rosli et al 2019) and uric acid (Gasse et al 2009, Braga et al 2017), can also activate NLRP3 and promote an excessive innate immune response. The activation of this disproportionate innate immune response in turn leads to the accumulation of pathogenic inflammatory monocyte-macrophages (IMMs), resulting in elevated lung cytokine/chemokine levels, vascular leakage, and tissue damage (Channappanavar et al 2016). Collectively, these observations provide a mechanistic basis for NLRP3 in excessive inflammation to coronavirus infection.

1.1.5 Inflammasome activation by mechanical ventilation and ARDS

In severe COVID-19, non-invasive and invasive mechanical ventilation is applied as a life supporting therapy. Mechanical stretch especially in the inflamed and stressed tissue is leading to eATP release. eATP is sensed by the purinergic receptor P2X7 leading to potent NLRP3 inflammasome activation (Eckle et al 2007, Matsuyama et al 2008). This cascade of events further amplifies tissue inflammation and ARDS. In mice, IL-18 expression is increased in the lungs after intraperitoneal administration of lipopolysaccharide (LPS) or the occurrence of hemorrhage (Kawayama et al 2012). Furthermore, a neutralizing anti-IL-18 antibody has been shown to reduce the lung inflammatory damage in a murine acute lung injury model (Abdel Fattah et al 2015).

1.1.6 Translational evidence that the NLRP3 inflammasome is activated in patients with coronavirus lung pathology

Infections with highly pathogenic respiratory viruses, such as SARS-CoV-1 and SARS-CoV-2, initiate a cytokine burst that causes acute lung injury and ARDS. Patients manifest lung injury at the time during which viral load is actually falling, indicating that, in humans, significant damage to the lungs is likely mediated by an excessive immune response rather than direct viral cytopathic effects.

One of the key cytokines driving inflammation in the bronchoalveolar space in patients with ARDS is IL-1 β (Pugin et al 1996). It enhances the production of other cytokines with a longer half-life, such as IL-6, which accumulates in a sustained manner during the disease and (Olman et al 2004, Zhang et al 2004) The pathogenic role of IL-1 β in the lungs is supported by findings in rat that transient lung expression of IL-1 β via adenoviral gene transfer causes a local increase of the pro-inflammatory cytokines IL-6 and TNF- α and a vigorous acute inflammatory tissue response, which then leads to progressive interstitial fibrogenesis (Kolb et al 2001).

Another cytokine that may have a pathogenic effect is IL-18. Levels of IL-18 are elevated in the serum of patients with SARS-CoV-1 (Huang et al 2005). IL-18 promotes lung fibrosis (Zhang et al 2019) and the production of Type 1 helper T cell cytokines that mediate alveolar epithelial cell death. Consistent with this hypothesis, the expression of IL-18 in the lung induces type 1, type 2, and type 17 cytokines and stimulates alveolar destruction causing vascular remodeling and airway fibrosis (Kang et al 2012). Interestingly, an interferon-gamma type cytokine storm was described post SARS coronavirus infection (Kawayama et al 2012). Thus, the existing data provide evidence for an important role of IL-18 in lung injuries of different origins.

1.1.7 Inflammasome in acute organ injury and sepsis

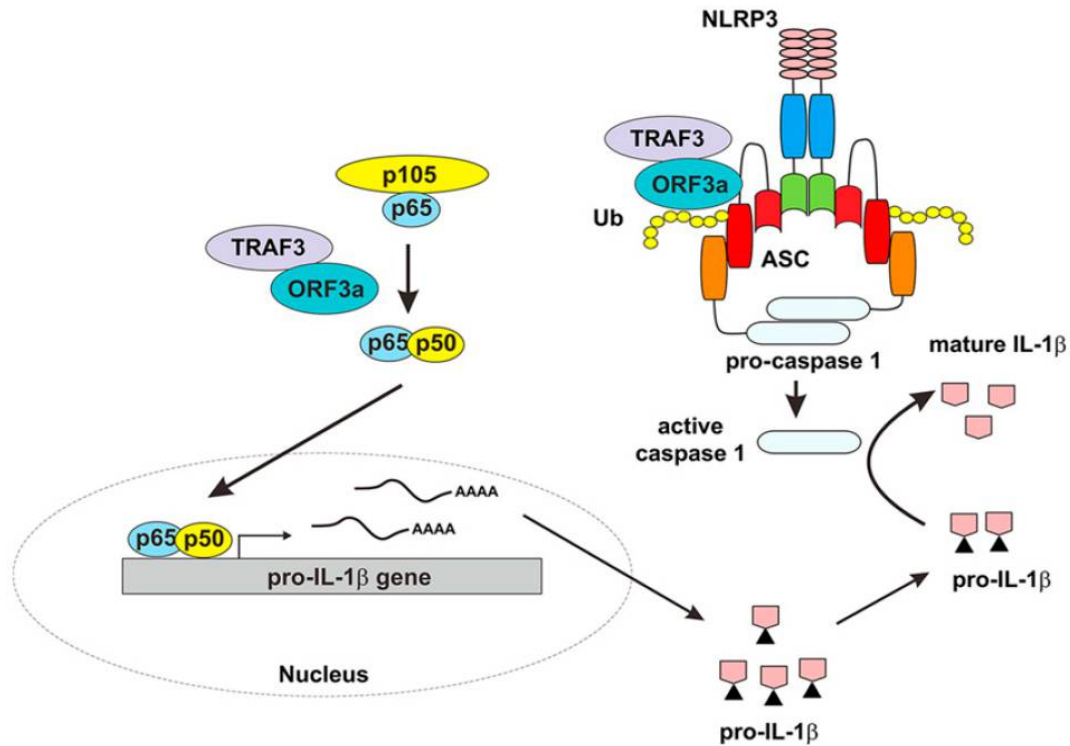
Beyond the acute and life-threatening respiratory complications severe COVID-19 patients develop acute kidney injury (AKI) and sepsis (Zhou et al 2020a) contributing significantly to overall mortality. NLRP3 inhibition in animal models of sepsis reduces inflammation and tissue damage, enhances phagocytosis, and leads to increased survival. (Jin et al 2017). Sepsis, tissue damage and suboptimal supply of oxygen to the kidney together with common comorbidities in severe COVID-19 patients such as hypertension and diabetes are increasing the risk of AKI. NLRP3 has been described to contribute to septic (Yang et al 2019), ischemia/reperfusion (Han et al 2020), virus (Liu et al 2019) and rhabdomyolysis (Komada et al 2015) induced AKI (Cao et al 2015). Furthermore, urinary IL-18 is one the earliest and most predictive markers for patients at risk of developing AKI (Parikh et al 2005). Amelioration of sepsis and AKI by NLRP3 inhibition may improve patients' "manageability" and thereby could increase overall survival.

1.1.8 Summary

The inflammasome and the pivotal mediators IL-1 β , IL-18 and NLRP3 are known contributors to the hyper-inflammatory response that results in severe pulmonary tissue damage after initial SARS-CoV-1 and SARS-CoV-2 infections. Treatment with a NLRP3 inhibitor in patients with severe COVID-19 pulmonary disease is expected to reduce inflammation, reverse lung pathology and may improve ventilation and clinical outcomes. Importantly, available evidence strongly supports the concept that these treatments would not increase viral persistence or other morbidity related to a SARS-CoV-2 infection especially when administered at the later stage of the disease as respiratory failure develops.

Figure 1-1 Working model for ORF3a-induced activation of the NLRP3 inflammasome

Note: On one hand, ORF3a interacts with TRAF3 to activate NF- κ B, resulting in transcription of the pro-IL-1 β gene. On the other hand, ORF3a interacts with TRAF3 to promote ASC ubiquitination, leading to activation of caspase 1 and IL-1 β maturation. ORF3a sufficiently activates both signals required for NLRP3 inflammasome activation. Ub, ubiquitin. Source: [Siu et al \(2019\)](#).



1.2 DFV890

Commercially Confidential Information

Commercially Confidential Information

1.3 Purpose

The purpose of this study is to evaluate the efficacy and safety of DFV890 in addition to current standard of care (SoC) compared with SoC alone in controlling the inflammatory syndrome and resultant ARDS in hospitalized patients presenting with COVID-19 pneumonia and impaired respiratory function. DFV890 CCI will be dosed CCI for 14 days.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	Endpoint(s) for primary objective(s)
<ul style="list-style-type: none"> To evaluate the effect of DFV890 in addition to SoC, compared with SoC alone, on the Acute Physiology and Chronic Health Evaluation II (APACHE II) score 	<ul style="list-style-type: none"> APACHE II severity of disease score on Day 15 or on day of discharge (whichever is earlier) with worst case imputation for death
Secondary Objective(s)	Endpoint(s) for secondary objective(s)
<ul style="list-style-type: none"> To evaluate the effect of DFV890 in addition to SoC, compared with SoC alone, on inflammatory status 	<ul style="list-style-type: none"> Serum C-reactive protein (CRP) levels
<ul style="list-style-type: none"> To evaluate the effect of DFV890 in addition to SoC, compared with SoC alone, on clinical status 	Endpoints based on the 9-point ordinal scale (Appendix 1): <ul style="list-style-type: none"> Survival without the need for invasive mechanical ventilation at Days 15 and 29 At least one level improvement in clinical status at Days 15 and 29 Clinical status over time
<ul style="list-style-type: none"> To evaluate the safety of DFV890 in addition to SoC, compared with SoC alone 	<ul style="list-style-type: none"> Number of participants with Adverse Events (AE), Serious Adverse Events (SAE), clinically significant changes in laboratory measures, and vital signs

Commercially Confidential Information

2.1 Primary estimands

The primary clinical question of interest is: What is the effect of DFV890 in addition to SoC versus SoC alone in SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function on APACHE-II severity of disease score taking into account early discharge from hospital or death but regardless of investigational treatment discontinuation?

The justification for the primary estimand is that it will capture the combined effect of investigational treatment in participants who remain in hospital for 14 days, the effect on early discharge within 14 days and the effect on death rate within 14 days, in a manner than reflects clinical practice.

The primary estimand is described by the following attributes:

1. Population: SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function. Further details about the population are provided in [Section 5](#).
2. Endpoint: APACHE II severity of disease score on Day 15 or on day of discharge (whichever is earlier) with worst case imputation for death. Participants who die on Day 15 or earlier will be assigned the highest observed APACHE II score of any of the participants at any time during the trial. Note this imputation for death takes precedence over the APACHE II score on day of discharge.
3. Treatment of interest: the randomized treatment (the investigational treatment DFV890 in addition to SoC or control treatment of SoC alone).

4. Handling of remaining intercurrent events: Treatment discontinuation for any reason will be ignored and thus follow a treatment policy strategy i.e. participants who discontinue treatment will be treated in the same manner as those that continue the treatment as planned.
5. Summary measure: The difference in variable means between treatments.

2.2 Secondary estimands

Not applicable.

3 Study design

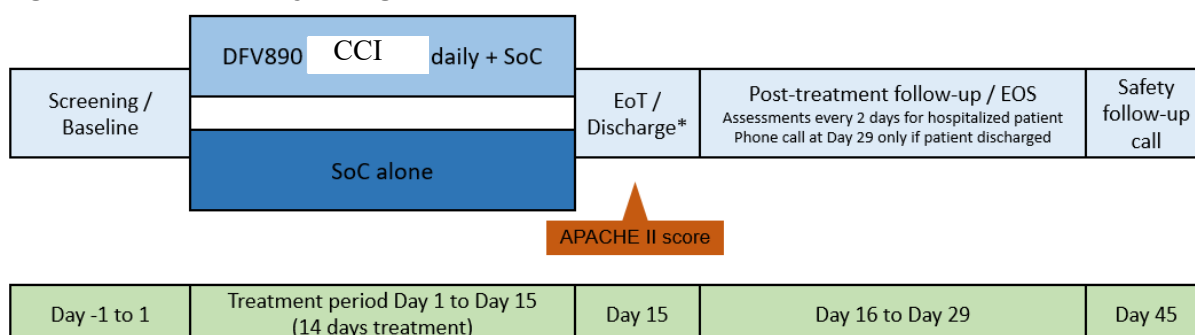
This is a Phase 2, randomized, controlled, open label multi-center study to assess the efficacy and safety of DFV890 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function (Figure 3-1).

Written informed consent will be obtained from participants before any study related assessments or procedures are performed. Thereafter, medications and eligibility criteria will be reviewed by study personnel. All participants signing informed consent must be registered by study staff in the Interactive Response Technology (IRT).

Assessments during the study will occur per the schedule of study assessments as described in Table 8-1.

Figure 3-1

Study design



*If participant discharged from hospital prior to Day 15, investigational treatment should be taken at home to complete the 14-day treatment period.

The study consists of four parts:

1. **Screening / Baseline visit** (Day -1 to 1): lasts up to a maximum of 24 hours and comprises a screening / baseline assessment. This visit will be used to confirm that the study inclusion and exclusion criteria are met and serves as baseline assessment prior to randomization. Those randomized to the DFV890 investigational treatment arm can commence administration with either the morning or evening dose, depending upon time of randomization. Baseline blood tests will be performed in all participants; those who screen fail because of study inclusion / exclusion criteria (e.g., serum CRP, liver function tests), will not undergo randomization.

2. **Treatment period** (Day 1-15): Participants in the investigational treatment arm will receive DFV890 CCI orally or via a nasogastric feeding tube administered for a total of 14 days CCI in addition to SoC. Study drug will be supplied in tablet form which can be crushed, allowing for both oral and nasogastric administration. Participants in the control arm will receive SoC alone.

Participants will be randomized as soon as possible, but within a maximum of 24 hours after screening in a 1:1 ratio to receive either DFV890 in addition to SoC or SoC alone.

Commercially Confidential Information

Study assessments will be conducted every 2 days for hospitalized participants.

The End of Treatment (EOT) visit will take place on Day 15. If participants are discharged from the hospital prior to Day 15, assessments on the day of discharge should be performed according to the schedule listed under Day 15; participants will continue to take the investigational treatment at home to complete the 14-day treatment period and the participants should return to the site for the Day 15/EOT assessment (all other visits between discharge and Day 15 can be omitted). If a hospital visit is not possible at Day 15, then home nursing services may be used to support this last visit where these are available in accordance with local guidelines and should include all possible assessments (e.g., oxygen saturation with portable monitors).

3. **Follow-up** (Day 16-29): After completion of the 14 day- treatment period, participants will be observed until Day 29 or discharged from hospital, whichever is sooner. Study assessments to be conducted every 2 days for hospitalized participants.

If participants are discharged from hospital prior to Day 29, a study visit conducted by telephone will occur on Day 29 (all other visits between discharge and Day 29 can be omitted).

4. **30-day safety follow-up assessment** (Day 45): A follow-up visit for safety will be conducted by telephone.

4 Rationale

4.1 Rationale for study design

This is a randomized, controlled, open-label, multicenter study in hospitalized adult patients (≥ 18 -80 years) with COVID-19-associated pneumonia and impaired respiratory function. This design supports the assessment of preliminary efficacy Commercially Confidential Information and safety of DFV890 in addition to SoC in this critically ill patient population.

The **Screening / Baseline visit** will be used to confirm that the study inclusion and exclusion criteria are met and for performing baseline clinical observations and biological sampling (blood, urine). Patients meeting the inclusion and exclusion criteria will be acutely unwell and it is anticipated that recruitment and randomization will take place relatively rapidly, with entry into the study taking place within a maximum of 24 hours of screening. This is justified based upon the clinical severity of illness in patients admitted with COVID-19 associated pneumonia and impaired respiratory function and their likelihood of deterioration shortly after hospital admission.

During the **Treatment period** participants will be randomized in a 1:1 ratio to receive either DFV890 CCI in addition to SoC or SoC alone for a total of 14 days. Randomization is justified as there is at present no clinical evidence that DFV890 will be efficacious in reducing disease severity in COVID-19 patients. The 1:1 randomization ratio was chosen to maximize the statistical power for the primary analysis whilst minimizing the overall sample size.

Commercially Confidential Information

The **Study Endpoints** measure clinical status, Commercially Confidential Information and laboratory values, including serum CRP, Commercially Confidential Information and safety during and after the 14-day treatment period. Commercially Confidential Information

4.2 Rationale for participant numbers and endpoint

The total sample size of 120 participants randomized in a 1:1 ratio to the two treatment groups allows for an adequate assessment on the chosen primary endpoint.

The primary endpoint for this study is the APACHE II score (range 0 to 71) on day 15 or on day of discharge (whichever is earlier) with worst case imputation for death as this disease severity score provides a comprehensive structured assessment of the clinical, physiological and laboratory parameters that have been routinely employed by physicians in the current situation to assess the overall clinical status of COVID-19 patients with pneumonia and respiratory failure (Yang et al 2020, Wang et al 2020). In particular, the APACHE II disease severity score captures the clinically relevant physiologic variables for an aggregate score, with higher scores indicating more severe disease, with a median score of 18 reported for non-survivors of COVID-19. The APACHE II score will not be used by investigators to direct medical management of participants in this study.

To establish clinical efficacy based on APACHE II score, a sample size of 60 participants per treatment group provides 80% power when testing on an 10% 1-sided alpha level under the assumption that DFV890 in addition to SoC reduces the APACHE II score by 3.6 points more than SoC alone (assumed standard deviation of 9.2 based on Wang et al (2020)). The type I error rate of 10% is considered an acceptable false positive risk for an exploratory study.

Other clinical endpoints such as those derived from the 9-point ordinal scale were considered as primary endpoints.

Commercially Confidential Information

4.3 Rationale for choice of background therapy

There is at present no health authority (HA) approved treatments for COVID-19 or its sequelae, including the cytokine storm which develops in those most severely affected. Current SoC in the European Union (EU) and United States of America (US) includes a variety of supportive therapies, ranging from the administration of supplementary oxygen to full intensive care support, alongside the use of antiviral agents and intravenous corticosteroids, though there is considerable inter-center variability regarding the use of these. Local SoC is permitted in all participants of the study, though every effort will be made by investigators to standardize this within individual centers.

Commercially Confidential Information

4.4 Rationale for dose/regimen and duration of treatment

The median hospital stay for COVID-19 has been reported to be 12 days with an interquartile range of 1 to 14 days (Cao et al 2020). Therefore, a duration of treatment for 14 days seems reasonable and was thus selected for this study.

Commercially Confidential Information

Commercially Confidential Information

4.5 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The study has been designed to compare the use of DFV890 in addition to SoC with SoC alone. Although there are no approved treatments for COVID-19, SoC therapy for patients with COVID-19 pneumonia includes a range of supportive care and anti-viral treatments with inter-center variability. There is no comparator or placebo therapy administered.

Commercially Confidential Information

SoC is therefore appropriate as the control for this study.

4.6 Purpose and timing of interim analyses/design adaptations

Commercially Confidential Information

4.7 Risks and benefits

4.7.1 Potential benefits and risks to study participants

Commercially Confidential Information

The participants enrolled in this study will have COVID-19-associated pneumonia, impaired respiratory function and evidence of an inflammation syndrome with a significant risk of the development of ARDS requiring prolonged mechanical ventilation and ICU stay to maintain life. Currently, apart from supportive medical care that is of limited benefit in this population, there are no approved therapeutics targeting the underlying inflammatory process to improve oxygenation, reverse respiratory failure and reduce the complications of SARS-CoV-2 infection to improve the overall clinical outcome.

4.7.2 Potential risks to participants

The risk to participants in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, frequent follow-up, minimal duration of the study, stopping rules and periodic review of safety data by an independent DMC.

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

4.7.3 Overall risk benefit

Commercially Confidential Information

In the context of the potential clinical benefit for patient population with limited effective therapeutic options, the overall safety profile of DFV890 is acceptable, and the benefit/risk favorable. In addition to the risks noted above, there may be risks to DFV890 that are serious and unforeseen. Therefore,

the risks to participants in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, frequent follow up, minimal duration of the study, stopping rule

Commercially Confidential Information

4.8 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 28 days, from each participant as part of the study. Approximately 190 mL blood will be collected over the first 15 days during which participants are hospitalized. For hospitalization of 28 days a total blood volume of approximately 250 mL will be collected. Sample volume may vary according to local laboratory standard. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the assessment schedule ([Table 8-1](#)).

Commercially Confidential Information

5 Study Population

The study population includes adult male and female SARS-CoV-2 infected patients who are hospitalized and diagnosed with COVID-19 pneumonia and impaired respiratory function.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Male and female patients aged 18-80 years inclusive at screening
2. Signed Informed Consent Form (ICF) by patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative (if allowed according to local requirements in participating countries excluding Germany)
3. Clinically diagnosed with the SARS-CoV-2 virus by polymerase chain reaction (PCR) or by other approved diagnostic methodology within 7 days prior to randomization
4. Hospitalized with COVID-19-induced pneumonia evidenced by chest X-ray, computed tomography scan (CT scan) or magnetic resonance scan (MR scan), taken within 5 days prior to randomization (within 24 hours in patients in the Netherlands)
5. Impaired respiratory function, defined as peripheral oxygen saturation (SpO_2) $\leq 93\%$ on room air or partial pressure of oxygen (PaO_2) / fraction of inspired oxygen (FiO_2) < 300 millimeter of mercury (mmHg) at time of screening. For cities located at altitudes greater than 2500 m above sea level, these will be substituted with $SpO_2 < 90\%$ and $PaO_2/FiO_2 < 250$ mmHg.
6. Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score of ≥ 10 at time of screening
7. CRP ≥ 20 mg/L and/or ferritin level ≥ 600 $\mu\text{g/L}$ at screening
8. Body mass index of ≥ 18 to < 40 kg/m^2 at screening
9. Ability to comply with the study protocol, in the investigator's judgment

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

Commercially Confidential Information

2. Suspected active or chronic bacterial (including *Mycobacterium tuberculosis*), fungal, viral, or other infection (besides SARS-CoV-2)
3. In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatment
4. Intubated prior to randomization
5. Patients who have explicitly expressed the wish not to receive intensive care support when this would be indicated based on their condition
6. Previous treatment with anti-rejection and immunomodulatory drugs within the past 2 weeks, or within the past 30 days or 5 half-lives (whichever is the longer) for immunomodulatory therapeutic antibodies or prohibited drugs (see [Section 6.2.1.2](#)), with the exception of hydroxychloroquine, chloroquine or corticosteroids:
 - For COVID-19 infection, ongoing corticosteroid treatment is permitted at doses as per local SoC
 - For non-COVID-19 disorders, ongoing corticosteroid treatment is permitted at doses up to and including prednisolone 10 mg daily or equivalent (see [Section 6.2.1](#))
 - In patients in the Netherlands only, the use of hydroxychloroquine and/or chloroquine in the past 2 weeks are exclusionary
7. Serum alanine transaminase (ALT) or aspartate transaminase (AST) >5 times upper limit of normal detected within 24 hours at screening or at baseline (according to local laboratory reference ranges) or other evidence of severe hepatic impairment (Child-Pugh Class C, see [Appendix 4](#))
8. Absolute peripheral blood neutrophil count of $\leq 1000/\text{mm}^3$
9. Estimated GFR (eGFR) $\leq 30 \text{ mL}/\text{min}/1.73\text{m}^2$ (based on CKD-EPI formula)

Commercially Confidential Information

11. Patients currently being treated with drugs known to be strong or moderate inducers of isoenzyme CYP2C9 and/or strong inhibitors of CYP2C9 and/or strong inducers of cytochrome P450, family 3, subfamily A (CYP3A) (see list of prohibited drugs: [Section 6.2.1.2](#)) and the treatment cannot be discontinued or switched to a different medication prior to starting study treatment
12. Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

Commercially Confidential Information

Commercially Confidential Information

15. Patients with innate Commercially Confidential Information
acquired immune deficiencies Commercially Confidential Information or
16. Patients who have undergone solid organ or stem cell transplantation

Commercially Confidential Information

18. Participation in any other clinical trials of investigational medicinal products.

6 Treatment

6.1 Study treatment

A separate Pharmacy Manual is not provided. The investigational treatment preparation for DFV890 is described in [Section 6.1.1](#) and [Section 6.7](#).

6.1.1 Investigational and control drugs

The study will enroll participants who require hospitalization and will receive either DFV890 in addition to the available SoC or the available SoC alone.

The investigational drug DFV890 will be prepared by the sponsor as 25 mg tablets. Investigational drug will be supplied to the investigator as open-label patient-specific kits.

- DFV890 CCI will be administered orally Commercially Confidential Information
Commercially Confidential Information Participants discharged prior to Day 15 will be provided with individual medication diary cards to record each administration of investigational treatment at home.
- If a participant becomes intubated during the course of the study, study drug can be administered as follows, according to the local SoC:
 - For participants unable to ingest tablets, study drug can be administered through a nasogastric tube (8 French or greater) as follows:
 - Suspend CCI in approximately 40 mL of water with stirring for approximately 3 minutes

- The suspension can then be administered through a nasogastric tube using an appropriate syringe. Commercially Confidential Information
- The tube should be rinsed with approximately 70 mL of water
- Duration of treatment is 14 days.

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
DFV890 25 mg	Tablet	Oral use	Open label patient specific kits; blisters	Sponsor (global)

6.1.2 Additional study treatments

Participants assigned to the DFV890 arm will receive DFV890 CCI in addition to SoC and participants assigned to the control arm will receive SoC alone. SoC administered beside the study treatment will be supplied by the investigational site. No other treatment beyond DFV890 is included in this study.

6.1.3 Treatment arms/group

Participants will be assigned at randomization to one of the following treatment arms/groups in a ratio of 1:1:

- DFV890 CCI + SoC for 14 days
- SoC alone for 14 days

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms (CRF).

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

If participants are discharged from hospital prior to Day 15, they must be told to notify the Treating Physician about any new medications he / she takes after the start of DFV890 investigational treatment.

During the course of the study, participants may receive anti-viral treatment (e.g., hydroxychloroquine, chloroquine, remdesivir, faripivavir, ritonavir, lopinavir), convalescent plasma containing high titres of anti SARS-CoV-2 antibodies, intravenous, oral or inhaled

corticosteroids (e.g. dexamethasone), antibiotics and other agents where these form part of SoC for the treatment of COVID-19 infection in their participating centre.

Participants are permitted to receive low-dose corticosteroids (up to a maximum of 10 mg/day prednisolone equivalent) for the treatment of non-COVID-19 disorders.

Commercially Confidential Information

The SoC will be administered according to the local practices and the known dosage recommendations, contraindications, warnings and interactions with other drugs must be observed for the drugs used concomitantly as SoC.

Whilst the protocol defines experimental immunomodulatory treatments including anti-IL-6 monoclonal antibodies as prohibited ([Section 6.2.1.2](#)), participants with significantly deteriorating clinical status may still receive such therapies in rescue situations where their treating physician is of the opinion that the potential benefit of such therapy outweighs the risks. In this situation participants receiving DFV890 therapy should immediately discontinue DFV890 (see [Section 6.2.1.2](#) and [Section 9.1.1](#)). However, these DFV890-treated participants, as well as those receiving experimental immunomodulatory therapies following completion of their 14-day treatment period with DFV890 and those in the control arm receiving SoC alone should remain in the study and the Investigator should continue collecting data on outcomes through the study visit schedule.

6.2.1.1 DFV890 potential for drug-drug interaction

Clinical studies to investigate drug-drug interactions with Cytochrome P450 (CYP) substrates/modulators and DFV890 have not been performed yet. Evaluation and recommendations are based on in vitro / preclinical data and physiology-based PK simulations, and there are no clinical data confirming whether such interactions will occur in participants.

DFV890 as a victim: DFV890 is expected to be eliminated mainly via hepatic CYP-mediated metabolism with CYP2C9 (68%) and CYP3A4 (30%) as the main contributing enzymes. DFV890 may therefore be affected by CYP2C9 and/or CYP3A4 interactions. Chronic dosing with dual CYP2C9/CYP3A4 inducers (e.g., 600 mg rifampicin) is expected to induce both enzymes, thereby increasing the risk of reducing DFV890 drug exposure by approximately 4-fold to sub-therapeutic levels. Co-administration of DFV890 with strong inhibitors of CYP2C9 (e.g., 200 mg fluconazole, or 2 g sulfaphenazole) is expected to reduce enzymatic metabolic capacity, thereby increasing the risk of increasing DFV890 drug exposure by approximately 3-fold. When dosed with strong CYP3A inhibitors, the DFV890 AUC is expected to increase on average by approximately 1.6-fold.

DFV890 as perpetrator: Due to its in vitro weak-to-moderate CYP3A4 induction potential, DFV890 can potentially decrease systemic exposure of sensitive CYP3A4 substrates by approximately 2-fold or some oral hormonal contraceptives (e.g., ethinylestradiol) by 20-30%.

In this proposed clinical study protocol, modulators (strong or moderate inducers and strong inhibitors) of CYP2C9 and/or strong inducers of CYP3A are prohibited ([Section 6.2.1.2](#)). Drugs that are metabolized by CYP3A or which are strong/moderate inhibitors of CYP3A should be used with caution ([Section 6.2.1.3](#)).

6.2.1.2 Prohibited drugs and herbal medications

- Experimental immunomodulatory therapies for the treatment of COVID-19, including, but not limited to canakinumab and other anti-IL-1 antibodies, tocilizumab and other anti-IL-6 antibodies, ruxolitinib and other JAK inhibitors, eculizumab and other complement inhibitors. Where any of these therapies are administered as rescue therapy or for any other reason, DFV890 must be immediately discontinued.
- Strong or moderate inducers of CYP2C9 or strong inducers of CYP3A including carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, mitotane and St. John's wort (*Hypericum perforatum*)
- Strong inhibitors of CYP2C9 including miconazole, berberine (herbal product), sulfaphenazole, fluconazole, resveratrol (herbal product)
- All investigational medications being concurrently used as part of another investigational clinical trial.

6.2.1.3 Drugs to be used with caution

DFV890 was identified *in vitro* as a substrate of CYP3A, so an increase in systemic exposure of DFV890 by not more than 1.6-fold when co-administered with strong or moderate CYP3A inhibitors such as antiviral drugs (e.g., ritonavir), antifungal (e.g., itraconazole, ketoconazole) and antibiotics (e.g., erythromycin, clarithromycin) cannot be ruled out. Investigators may, at their discretion, co-administer known inhibitors of CYP3A, but their duration should be kept as short as possible, and participants must be closely monitored.

In vitro metabolism studies showed that DFV890 might have the potential to induce the metabolism of drug substrates metabolized by isoenzyme CYP3A by up to 2-fold. Investigators at their discretion may administer concomitant medications known to be metabolized by CYP3A4/5. Participants receiving such medications may require dose titration or increase of the concomitant drug. Particularly, caution is advised when DFV890 is co-administered with drugs that are sensitive substrates of CYP3A and/or have a narrow therapeutic index.

Table 6-2 Concomitant medications to be used with caution

Category	Drug Names
Strong inhibitors of CYP3A	ombitasvir/paritaprevir/dasabuvir/ritonavir, indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, elvitegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
Moderate inhibitors of CYP3A	aprepitant, amprenavir, atazanavir, cimetidine, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, grapefruit juice, imatinib, isavuconazole, netupitant, nilotinib, tofisopam, verapamil
Narrow therapeutic index substrates of CYP3A	alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, ergotamine, fentanyl, pimozone, quinidine, sirolimus, tacrolimus
Sensitive substrates of CYP3A	alfentanil, alpha-dihydroergocryptine, aprepitant, atazanavir, atorvastatin, avanafil, bosutinib, brotizolam, budesonide, buspirone, cobimetinib, conivaptan, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutinib, indinavir, isavuconazole, ivabradine, ivacaftor, levomethadyl acetate, lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, paritaprevir, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, tacrolimus, ticagrelor, tilidine, tipranavir, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the ICF, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.3.2 Treatment assignment, randomization

At randomization visit, all eligible participants will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms. A randomization list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

Commercially Confidential Information

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Treatment will be open to participants, investigator staff/persons performing the assessments and the Novartis study team.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted without consultation with Novartis.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Treatment will be recorded on the appropriate electronic Case Report Form (eCRF).

For investigational treatment administration at home the investigator must promote compliance by instructing the participant to take the investigational treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the investigational treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the participant. This information should be captured in the source document at each visit. All investigational treatment dispensed and returned must be recorded in the Drug Accountability Log.

Commercially Confidential Information

6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs) in this patient population. Commercially Confidential Information

CCI AKI is common in patients with severe COVID-19. Treatment is supportive, with the institution of renal replacement therapy where this is indicated.

Medication used to treat AEs must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

Not applicable. This is an open-label study and the treatment allocation will be known to participants, investigators and the Novartis team.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section ([Section 6.1.1](#)).

A unique medication number is printed on the study medication label.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all investigational treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

Medication labels will be in the local language (or in English in case allowed according to local regulation) and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants discharged prior to Day 15 will be asked to return all unused investigational treatment and packaging at the end of the study or at the time of discontinuation of investigational treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

Table 6-3 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
DFV890 25 mg	CCI	Daily CCI (14 days)

Participants should take DFV890 CCI at approximately the same time each day

Commercially Confidential Information

Participants discharged prior to Day 15 will be provided with individual medication diary cards to record each administration of investigational treatment at home. These will be checked regularly by site staff.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB) / Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements in participating countries excluding Germany), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is, or becomes capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document. The consenting process for all study participants will be performed according to the applicable local regulations and described in the ICF.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed ICF that complies with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also includes:
 - Commercially Confidential Information
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- Commercially Confidential Information

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

Commercially Confidential Information

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule ([Table 8-1](#)) lists all assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule ([Table 8-1](#)) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. If participant is prematurely discontinued from the study at any visit before Day 15, then assessments of EOT visit should be performed and if participant is prematurely discontinued at any visit after Day 15, then assessments of EOS visit should be performed. At the final EOT visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Table 8-1 Assessment schedule

Period	Screening / Baseline / Treatment	Treatment ^{2, 3, 12}								Post-Treatment Follow-up	Safety follow-up	
Visit Name	Screening / Baseline / Treatment ¹⁶	Treatment							EOT ¹⁴ / Discharge ⁴	Follow-up ⁵ (if hospitalized assessments performed at site every 2 days; if discharged only telephone call on Day 29)	30-days safety follow-up (post last treatment) ¹⁵	
Days	-1 to 1	2	4	6	8	10	12	14	15 (+2 days)	17, 19, 21, 23, 25, 27	29 / EOS (-1/+3 days)	45 (+/-3 days)
Domiciled (as required)	X	X	X	X	X	X	X	X	X	X	X	
Informed consent Commercially Confidential Information	X ¹											
Inclusion / Exclusion criteria	X											
Demography	X											
Medical history/current medical conditions	X											
Presence SARS-CoV-2 virus / viral load ⁶	X	Commercially Confidential Information										
Chest X-ray (CXR), CT or MR scan ⁶	X								X ¹³			
Randomization (IRT)	X											
Physical examination	S								S		S	
Vital signs ⁷	X	X	X	X	X	X	X	X	X	X	X	
Respiratory status (spont. breathing, FiO2, ventilator parameters, ECMO), fluid balance, need for RRT	X	X	X	X	X	X	X	X	X	X	X	
APACHE II Commercially Confidential Information	X	X	X	X	X	X	X	X	X	X	X	
Clinical Status Evaluation with 9-category ordinal scale	X	X	X	X	X	X	X	X	X	X	X	
Weight and Height ⁸	X				X				X			

Period	Screening / Baseline / Treatment	Treatment ^{2, 3, 12}								Post-Treatment Follow-up	Safety follow-up		
Visit Name	Screening / Baseline / Treatment ¹⁶	Treatment							EOT ¹⁴ / Discharge ⁴	Follow-up ⁵ (if hospitalized assessments performed at site every 2 days; if discharged only telephone call on Day 29)	30-days safety follow-up (post last treatment) ¹⁵		
Days	-1 to 1	2	4	6	8	10	12	14	15 (+2 days)	17, 19, 21, 23, 25, 27	29 / EOS (-1/+3 days)	45 (+/-3 days)	
ECG evaluation (local)	X								X				
Commercially Confidential Information													
Blood chemistry including CRP, CCI ⁹	X	X	X	X	X	X	X	X	X	X	X		
Hematology (local lab) ⁹	X	X	X	X	X	X	X	X	X	X	X		
Coagulation (local lab) ⁹	X	X	X	X	X	X	X	X	X	X	X		
Commercially Confidential Information													
Commercially Confidential Information													
Drug administration record (DFV890)	X CCI	X											
Concomitant medications/Therapies including inotropic support	X	X	X	X	X	X	X	X	X	X	X		
Adverse events/serious adverse events	X	X											
Safety Follow up Call											X	S	
X = assessment to be recorded in the clinical database or received electronically from a vendor S = assessment to be recorded in the source documentation only 1. Informed consent must be signed prior to any study-related procedure.													

Period	Screening / Baseline / Treatment	Treatment ^{2, 3, 12}							Post-Treatment Follow-up	Safety follow-up		
Visit Name	Screening / Baseline / Treatment ¹⁶	Treatment							EOT ¹⁴ / Discharge ⁴	Follow-up ⁵ (if hospitalized assessments performed at site every 2 days; if discharged only telephone call on Day 29)	30-days safety follow-up (post last treatment) ¹⁵	
Days	-1 to 1	2	4	6	8	10	12	14	15 (+2 days)	17, 19, 21, 23, 25, 27	29 / EOS (-1/+3 days)	45 (+/-3 days)
<p>2. Study treatment may start immediately after obtaining the screening/baseline measurements and confirming eligibility and is administered for a total 14 days. Commercially Confidential Information</p> <p>3. If a participant is discharged prior to Day 15 (this will be considered as Early Discharge visit), study medication should be administered at home to complete the 14 days treatment.</p> <p>4. If a participant is discharged prior to Day 15, then assessments on the day of discharge should be performed according to the schedule listed under Day 15 and participant should return to the site for the Day 15/EOT assessment (if hospital visit is not possible, then home nursing allowed). A visit window of +2 days is allowed for participants discharged prior to Day 15. Visits between day of discharge and Day 15 can be omitted.</p> <p>5. If a participant is discharged prior to Day 29 during the follow-up period (this will be considered as Discharge visit), then assessments on the day of discharge should be performed according to the schedule listed under Day 29. Participant will be contacted by telephone on Day 29 and only follow-up call, AE/SAE and concomitant medication/therapies information will be collected in the CRF. Visits between day of discharge and Day 29 can be omitted. If a participant is still hospitalized, all assessments should be performed every 2 days until Day 29 at the site.</p> <p>6. Results confirming positive SARS-CoV-2 virus by PCR or by other approved diagnostic methodology available within 7 days and chest X-ray, CT or MRI scan within 5 days prior to randomization may be used for eligibility.</p> <p>7. Vital signs include heart rate, respiratory rate (if not on mechanical ventilation), systolic and diastolic blood pressure and body temperature. Oxygen saturation (if not on mechanical ventilation), PaO₂/FiO₂ (if arterial, capillary or alternative blood gas measured) should be measured at the same time as the vital sign measurements.</p> <p>8. Height will be measured only at Screening/Baseline/Treatment visit. If not possible to measure height, it can be reported by the participant.</p> <p>9. Hematology, coagulation and blood chemistry including CRP, Commercially Confidential Information should be measured by the local laboratory.</p> <p>10.</p> <p>11. Commercially Confidential Information</p> <p>12. During the treatment period, all assessments should be performed in the morning pre-dose.</p> <p>13. Chest X-ray, CT or MRI scan at Day 15 (or on day of discharge if prior to Day 15) will be collected only if performed according to local SoC and if visit at the hospital is possible. The same method should be used at Day 15 (or on day of discharge if prior to Day 15) as was used at study entry.</p> <p>14. If participant is discharged prior to Day 15, home nursing services can be considered and should include all possible assessments (e.g., oxygen saturation with portable monitors).</p> <p>15. Safety follow-up call will be performed 30-days after last study treatment together with SAE data collection.</p> <p>16. All procedures performed as part of local standard of care in this hospitalization, prior to the patient being enrolled into the trial, may be used for screening/baseline assessments provided that they were performed on the same day that the patient was enrolled in the trial.</p>												

8.1 Screening

It is permissible to re-screen a participant once if s/he fails the initial screening.

In the case where a safety laboratory assessment at screening/initial baseline is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

8.1.1 Information to be collected on screening failures

Participants who sign an ICF and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see [Section 10.1.3](#) for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by HA.

8.2.1 Demographic information

Demographic data to be collected at screening on all participants include: year of birth or age, gender, race, ethnicity Commercially Confidential Information

Any relevant medical history including date of onset of COVID-19 disease symptoms, date of diagnosis of COVID-19 disease protocol solicited medical history, and/or current medical conditions before obtaining informed consent will be recorded in the Medical History CRF. Significant findings that are observed after the participant has provided informed consent and that meet the definition of an AE must also be recorded in the AE CRF. Whenever possible, diagnoses and not symptoms will be recorded.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.2.2 Prior and concomitant medications

Relevant prior and concomitant medications will be captured at the screening visit. Any changes to the ongoing medications or any new concomitant medications will be recorded in CRF on an ongoing basis throughout study participation.

8.3 Efficacy

Samples will be collected at the timepoints defined in the Assessment Schedule ([Table 8-1](#)) and will be obtained and evaluated in all participants at all dose levels, including the SoC treatment arm.

8.3.1 APACHE II severity of disease score

APACHE II (Acute Physiology And Chronic Health Evaluation) records various parameters grouped in vital signs, oxygenation, chemistry and hematology; in addition age and Glasgow Coma score is part of the APACHE II score ([Knaus et al 1985](#)) ([Table 16-4](#)). The worst value for each parameter in the last 24 hours will be entered in the CRF. Parameters for APACHE II will be recorded at screening/baseline, Day 2 and then every other day until Day 29 for hospitalized participants irrespective of ICU admission. The score will be recorded only for the screening/baseline visit in the CRF.

Blood gas measurement is required for completion of the APACHE II Score (PaO₂ alone where the FiO₂ is <50% or where the participant is not intubated, and PaO₂ and PaCO₂ for calculation of A-a O₂ gradient where FiO₂ is ≥50% or the participant is intubated). Where participants have an arterial line sited, an arterial blood sample should be used. Participants without an arterial line sited should have either an arterial, capillary or alternative blood sample collected.

8.3.2 Clinical status (9-point ordinal scale)

Assessment of clinical status using a 9-point ordinal scale ([WHO 2020](#)) will be recorded at screening/baseline, Day 2 and then every other day until Day 29 for hospitalized participants ([Appendix 1](#)). If a participant is discharged from the hospital, the assessment will be made by phone on the visit dates noted in [Table 8-1](#). Each day, the worse score for the previous day will be recorded, i.e. on Day 3, Day 2 score is obtained and recorded as Day 2.

8.3.3 CRP

Blood samples will be collected according to the Assessment Schedule ([Table 8-1](#)), performed locally and recorded in the CRF.

8.3.4 Appropriateness of efficacy assessments

The efficacy endpoints selected for this study are clinically relevant and in keeping with those employed in other studies of patients with COVID-19 pneumonia ([WHO 2020](#)).

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed (see [Table 8-1](#)).

For details on AE collection and reporting, refer to AE section ([Section 10.1](#)).

8.4.1 Laboratory evaluations

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Laboratory evaluations will be performed by the local laboratory.

8.4.2 Special clinical laboratory evaluations

All abnormal laboratory results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those laboratory adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Safety clinical laboratory tests will be performed locally (see [Table 8-2](#)) and recorded in the CRF.

Table 8-2 Clinical laboratory tests (locally)

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin (ALB), Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase, Total Bilirubin (TBL), Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting), CRP <small>Commercially Confidential Information</small>
Coagulation*	Prothrombin time (PT), International normalized ratio [INR]), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)
Pregnancy Test	Urine/Serum pregnancy test (refer to Section 8.4.7)

*Coagulation assessment should include only those tests routinely performed according to local standard of care.

8.4.3 Physical examination

A complete physical examination will be performed according to the Assessment Schedule ([Table 8-1](#)).

This will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made

after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

8.4.4 Vital signs

Vital sign measurements include respiratory rate, pulse rate (PR), systolic and diastolic blood pressure, and body temperature. Peripheral oxygen saturation on room air should also be measured at the same time as the vitals. For participants requiring supplemental oxygen, the oxygen flow rate (L/min) and/or FiO₂ should be recorded.

Vital signs will include the collection of body temperature (recorded in °C) as per local practice, blood pressure (BP) and pulse measurements.

8.4.5 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in [Table 8-1](#).

If height cannot be measured, the value reported by the participant will be entered in the CRF.

Body mass index (BMI) will be calculated using the following formula:

- $BMI = \text{Body weight (kg)} / [\text{Height (m)}]^2$

The Screening Visit height measurement will be used for BMI calculations throughout the study.

8.4.6 Electrocardiogram (ECG)

ECG assessments will be taken locally.

ECGs must be recorded after 10 minutes of rest in the supine position to ensure a stable baseline. In the case of a series of assessments, ECG should be first assessment obtained while the participant is at rest.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

Single 12-lead ECGs are to be collected with ECG machines available at the site. Single 12-lead ECGs are collected, and results are entered into the appropriate eCRF page. The original ECGs on non-heat-sensitive paper, appropriately signed, must be collected and archived at the study site. Alternatively 5-lead ECGs are allowed to be collected if 12-lead ECG is not available.

If an ECG performed as local SoC on the day of screening is utilized as part of the screening assessment, then the same diagnostic method (e.g. 5-lead or 12-lead) should be used consistently thereafter throughout the trial.

Each ECG tracing must be labeled with study number, participant's initials, Participant No., date and time, and filed in the study site source documents.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF as appropriate. If necessary, a cardiologist may be consulted.

8.4.7 Pregnancy and assessments of fertility

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner.

Commercially Confidential Information

8.4.7.1 Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

8.4.8 Chest X-ray

A standard chest X-ray (posteroanterior (PA) view) (CXR), chest CT or MR scan, will be performed as per standard local practice to diagnose pneumonia; except for those who have had a valid test done within 5 days of randomization (within 24 hours in patients in the Netherlands). The radiological examination performed at Day 15 (or on day of discharge if prior to Day 15) will be collected only if performed according to local SoC and if visit at the hospital is possible. The same method should be used at Day 15 (or on day of discharge if prior to Day 15) as was used at study entry.

Additional assessments may be performed, as needed.

Results from chest X-ray, CT scan or MR scan will be recorded in the CRF.

8.4.9 Appropriateness of safety measurements

The safety assessments selected are appropriate for this protocol which utilizes a compound which has not previously been used in a patient population and where the safety profile has not therefore been established. The assessments are relevant to the critical care setting and will enable determination of both safety therapeutic response in this setting.

8.5 Additional assessments

8.5.1 SARS-CoV-2 virus testing

SARS-CoV-2 virus to be measured using PCR at Screening (except for those who have had a valid test done within 7 days of randomization), Commercially Confidential Information

Documentation of the method used should be available in the source notes.

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section ([Section 6.2.1.2](#)), including where these treatments are administered as 'rescue' therapy
- Serum total bilirubin, ALT or AST are consistently elevated >10 times the upper limit of normal confirmed on two consecutive measurements that are performed at least 24 hours apart
- Any situation in which study participation might result in a safety risk to the participant
- Emergence of adverse events that in the judgment of the investigator, taking into account the participant's overall status, prevent the participant from continuing participation in the study
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study
- Severe hypersensitivity reaction occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, and hypotension.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see [Section 9.1.2](#)). Where possible, they should return for the assessments indicated in the Assessment Schedule ([Table 8-1](#)). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section ([Section 9.1.3](#)). This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

Participants who withdraw from the study will not be replaced.

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study-related contacts

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent and record this information.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Study stopping rules

Commercially Confidential Information

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date

of that decision (e.g., Each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

All randomized and/or treated participants should have a safety follow-up call conducted 30 days after last administration of investigational treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in [Section 10.1.3](#). Documentation of attempts to contact the participant should be recorded in the source documentation.

Continuing care should be provided by the investigator and/or referring physician based on participant availability for follow-up.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to [Section 10.1.2](#)):

1. Severity grade:
 - mild: usually transient in nature and generally not interfering with normal activities
 - moderate: sufficiently discomforting to interfere with normal activities
 - severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of

underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant

3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see [Section 10.1.2](#) for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. Its outcome (i.e. recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued until the end of study.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

10.1.2 Serious adverse events

A Serious Adverse Event (SAE) is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical condition(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
 - social reasons and respite care in the absence of any deterioration in the participant's general condition
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as “medically significant.” Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the last study visit must be reported to Novartis safety immediately, without undue delay, under no circumstances later than 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Screen Failures (e.g. a participant who is screened but is not treated or randomized): SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, under no circumstances later than 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis immediately, without undue delay, under no circumstances later than 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy outcomes will be followed-up at the following times:

- 1 month after the estimated date of delivery,
- 3 months after the estimated date of delivery (for a live birth only), and
- 12 months after the estimate date of delivery (for a live birth only).

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Investigational treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the investigational treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections ([Section 10.1.1](#), [Section 10.1.2](#), [Section 10.1.3](#)).

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to [Table 16-2](#) in [Appendix 2](#) for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in [Table 16-3](#) should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in [Table 16-3](#). Repeat liver chemistry tests (i.e., ALT, AST, TBL), prothrombin time/international normalized ratio (PT/INR), alkaline phosphatase (ALP) and GGT) to confirm elevation.

- These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
-

Commercially Confidential Information

- Hospitalization of the participant if appropriate
- Causality assessment of the liver event

- Thorough follow-up of the liver event should include
 - Based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2.2 Data Monitoring Committee

Commercially Confidential Information

11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated Clinical Research Organization) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature

of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Screenings, randomizations, exit statuses, as well as randomization codes and data about all treatment arms assigned to the participant will be tracked using an Interactive Response Technology (IRT).

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource Direct Data Entry (DDE) or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that investigational treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis clinical research associate organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original ICF signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Source data verification may be done on-site, if possible, or remotely, if the field monitor does not have access or have limited access to the site due to the current COVID-19 pandemic. Different approaches can be used depending on site medical records, and some of them could include sharing the information through electronic systems or platforms provided

by a third party. In all cases investigator and sponsor must adhere to the recommendations established by the applicable Health Authorities.

Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation. The analysis will be conducted on all participant data at the time the trial ends.

12.1 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) randomized.

The Safety analysis set will include all randomized participants.

Commercially Confidential Information

The PD analysis set will include all randomized participants with no protocol deviations with relevant impact on PD data.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be listed and summarized by system organ class and preferred term by treatment group.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to DFV890 will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment group.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary aim of the study is to evaluate the effect of DFV890 in addition to SoC compared with SoC alone on the APACHE II score. A decrease in the score is considered a favorable outcome.

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary estimand, including the primary endpoint is defined in [Section 2.1](#) of this protocol. It is based on the APACHE-II score.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary endpoint will be analyzed by an analysis of covariance model including treatment group and the three stratification factors as factors and baseline APACHE-II score as a covariate. The analysis will be performed on the safety analysis set. The mean differences of DFV890 in addition to SoC vs SoC alone will be reported with 90% confidence intervals (CIs). The 1-sided p-value for the overall treatment factor will be reported.

The primary objective will be achieved if the null hypothesis that DFV890 in addition to SoC is not different to SoC alone is rejected using a one side alpha of 10%.

12.4.3 Handling of remaining intercurrent events of primary estimand

As described in [Section 2.1](#), discontinuation of study treatment for any reason will be ignored.

12.4.4 Handling of missing values not related to intercurrent event

Handling of missing APACHE II scores or components of APACHE II scores at Day 15 or on day of discharge will be specified in the Statistical Analysis Plan.

12.4.5 Sensitivity analyses for primary endpoint/estimand

If there are imbalances in demographic or baseline characteristics between the two treatment groups, then an ANCOVA model similar to the primary analysis model with the additional inclusion of these demographic or baseline characteristics as covariates may be fitted.

12.4.6 Supplementary analysis

Not applicable

12.4.7 Supportive analyses

Not applicable

12.5 Analysis of secondary endpoints/estimands

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be provided for variables that are of the numeric or continuous type, while frequency distributions (with number and percent) will be provided for categorical variables.

Analyses of the hospital outcomes will be fully specified in the SAP.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of randomization to Day 29.

12.5.2.1 Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of randomized treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events and other significant adverse events leading to discontinuation.

12.5.2.2 Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

12.5.2.3 ECGs

PR, QRS, QT, QTcF, and RR intervals will be obtained from ECGs (12- or 5-lead) for each participant during the study. ECG data will be read and interpreted locally.

Categorical analysis of QT/QTcF interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTcF intervals or changes from baseline will be presented. In addition, a listing of these participants will be produced by treatment group.

All ECG data will be listed by treatment group, participant and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

12.5.2.4 Clinical laboratory evaluations

All laboratory data will be listed by treatment group, participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Serum CRP levels will be analyzed on a log-scale fitting a repeated measures mixed model including treatment group, study day, the three stratification factors and log transformed baseline CRP as a covariate. Interactions between study day and each of the terms in the model will also be included. The back-transformed ratios of DFV890 in addition to SoC vs SoC alone will be reported with 90% CIs. The 1-sided p-value for the overall treatment factor will be reported.

Commercially Confidential Information

12.6 Analysis of exploratory endpoints

Commercially Confidential Information

Commercially Confidential Information

12.8 Interim analyses

Commercially Confidential Information

12.9 Sample size calculation

12.9.1 Primary endpoint(s)

To establish clinical efficacy based on APACHE II score a sample size of 60 participants per treatment group provides 80% power when testing on an 10% 1-sided alpha level under the assumption that DFV890 in addition to SoC reduces the APACHE II score by 3.6 points more than SoC alone (assumed standard deviation of 9.2 based on [Wang et al \(2020\)](#)).

12.9.2 Secondary endpoint(s)

For the analysis of CRP a sample size of 60 participants per treatment group provides 80% power when testing on an 1% 1-sided alpha level under the assumption that DFV890 in addition to SoC reduces CRP by 44% more than SoC alone (assumed CV of 1.3 based on the range of variability observed in [Chen et al \(2020\)](#) and previous studies with canakinumab).

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written ICF, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the CSR the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.) .

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures (SOPs) as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and HAs, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request.

Abdel Fattah E, Bhattacharya A, Herron A, et al (2015) Critical role for IL-18 in spontaneous lung inflammation caused by autophagy deficiency. *J Immunol*; 194(11):5407-16.

Ahn M, Anderson DE, Zhang Q, et al (2019) Dampened NLRP3-mediated inflammation in bats and implications for a special viral reservoir host. *Nat Microbiol*; 4(5):789-99.

Belkaya S, Michailidis E, Korol CB, et al (2019) Inherited IL-18BP deficiency in human fulminant viral hepatitis. *J Exp Med*; 216(8):1777-90.

Braga TT, Forni MF, Correa-Costa M, et al (2017) Soluble uric acid activates the NLRP3 inflammasome. *Sci Rep*; 7:39884.

Cameron LA, Taha RA, Tsiopoulos A, et al (1999) Airway epithelium expresses interleukin-18. *Eur Respir J*; 14(3):553-9.

Cao B, Wang Y, Wen D, et al (2020) A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*.

Cao Y, Fei D, Chen M, et al (2015) Role of the nucleotide-binding domain-like receptor protein 3 inflammasome in acute kidney injury. *FEBS J*; 282(19):3799-807.

Channappanavar R, Fehr AR, Vijay R, et al (2016) Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. *Cell Host Microbe*; 19(2):181-93.

Chen IY, Moriyama M, Chang MF, et al (2019) Severe Acute Respiratory Syndrome Coronavirus viroporin 3a activates the NLRP3 inflammasome. *Front Microbiol*; 10:50.

Chen N, Zhou M, Dong X, et al (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*; 395(10223):507-13.

Coates BM, Staricha KL, Ravindran N, et al (2017) Inhibition of the NOD-like receptor protein 3 inflammasome is Protective in juvenile Influenza A virus infection. *Front Immunol*; 8:782.

Commercially Confidential Information

Eckle T, Fullbier L, Wehrmann M, et al (2007) Identification of ectonucleotidases CD39 and CD73 in innate protection during acute lung injury. *J Immunol*; 178(12):8127-37.

EMA (2020) Guidance on the management of clinical trials during the Covid-19 (coronavirus) pandemic. Brussels: EC (European Commission), EMA (European Medicines Agency), Head of Medicines Agencies (HMA), Version 3, 28 April 2020.

FDA (2003) Guidance for Industry - Pharmacokinetics in patients with impaired hepatic function: study design, data analysis, and impact on dosing and labeling. Rockville, MD: Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2003.

Ferrucci L, Corsi A, Lauretani F, et al (2005) The origins of age-related proinflammatory state. *Blood*; 105(6):2294-9.

Franchi L, Eigenbrod T, Munoz-Planillo R, et al (2014) Cytosolic double-stranded RNA activates the NLRP3 inflammasome via MAVS-induced membrane permeabilization and K⁺ efflux. *J Immunol*; 193(8):4214-22.

Gasse P, Riteau N, Charron S, et al (2009) Uric acid is a danger signal activating NALP3 inflammasome in lung injury inflammation and fibrosis. *Am J Respir Crit Care Med*; 179(10):903-13.

Han SJ, Lovaszi M, Kim M, et al (2020) P2X4 receptor exacerbates ischemic AKI and induces renal proximal tubular NLRP3 inflammasome signaling. *FASEB J*; 34(4):5465-82.

Horvath GL, Schrum JE, De Nardo CM, et al (2011) Intracellular sensing of microbes and danger signals by the inflammasomes. *Immunol Rev*; 243(1):119-35.

Huang KJ, Su IJ, Theron M, et al (2005) An interferon-gamma-related cytokine storm in SARS patients. *J Med Virol*; 75(2):185-94.

Ichinohe T, Lee HK, Ogura Y, et al (2009) Inflammasome recognition of influenza virus is essential for adaptive immune responses. *J Exp Med*; 206(1):79-87.

Jia X, Liu B, Bao L, et al (2018) Delayed oseltamivir plus sirolimus treatment attenuates H1N1 virus-induced severe lung injury correlated with repressed NLRP3 inflammasome activation and inflammatory cell infiltration. *PLoS Pathog*; 14(11):e1007428.

Jin L, Batra S, Jeyaseelan S (2017) Deletion of Nlrp3 augments survival during polymicrobial sepsis by decreasing autophagy and enhancing phagocytosis. *J Immunol*; 198(3):1253-62.

Kang MJ, Choi JM, Kim BH, et al (2012) IL-18 induces emphysema and airway and vascular remodeling via IFN-gamma, IL-17A, and IL-13. *Am J Respir Crit Care Med*; 185(11):1205-17.

Kawayama T, Okamoto M, Imaoka H, et al (2012) Interleukin-18 in pulmonary inflammatory diseases. *J Interferon Cytokine Res*; 32(10):443-9.

Commercially Confidential Information

Knaus WA, Draper EA, Wagner DP, et al (1985) APACHE II: a severity of disease classification system. *Crit Care Med*; 13(10):818-29.

Kolb M, Margetts PJ, Anthony DC, et al (2001) Transient expression of IL-1beta induces acute lung injury and chronic repair leading to pulmonary fibrosis. *J Clin Invest*; 107(12):1529-36.

Komada T, Usui F, Kawashima A, et al (2015) Role of NLRP3 inflammasomes for rhabdomyolysis-induced acute kidney injury. *Sci Rep*; 5:10901.

Commercially Confidential Information

Liu T, Tang L, Tang H, et al (2019) Zika virus infection induces acute kidney injury through activating NLRP3 inflammasome via suppressing Bcl-2. *Front Immunol*; 10:1925.

Commercially Confidential Information

Matsuyama H, Amaya F, Hashimoto S, et al (2008) Acute lung inflammation and ventilator-induced lung injury caused by ATP via the P2Y receptors: an experimental study. *Respir Res*; 9:79.

McAuley JL, Tate MD, MacKenzie-Kludas CJ, et al (2013) Activation of the NLRP3 inflammasome by IAV virulence protein PB1-F2 contributes to severe pathophysiology and disease. *PLoS Pathog*; 9(5):e1003392.

Commercially Confidential Information

Nieto-Torres JL, DeDiego ML, Verdia-Baguena C, et al (2014) Severe acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. *PLoS Pathog*; 10(5):e1004077.

Nieto-Torres JL, Verdia-Baguena C, Jimenez-Guardeno JM, et al (2015) Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. *Virology*; 485:330-9.

Olman MA, White KE, Ware LB, et al (2004) Pulmonary edema fluid from patients with early lung injury stimulates fibroblast proliferation through IL-1 beta-induced IL-6 expression. *J Immunol*; 172(4):2668-77.

Parikh CR, Abraham E, Ancukiewicz M, et al (2005) Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. *J Am Soc Nephrol*; 16(10):3046-52.

Pugin J, Ricou B, Steinberg KP, et al (1996) Proinflammatory activity in bronchoalveolar lavage fluids from patients with ARDS, a prominent role for interleukin-1. *Am J Respir Crit Care Med*; 153(6 Pt 1):1850-6.

Ren R, Wu S, Cai J, et al (2017) The H7N9 influenza A virus infection results in lethal inflammation in the mammalian host via the NLRP3-caspase-1 inflammasome. *Sci Rep*; 7(1):7625.

Rosli S, Kirby FJ, Lawlor KE, et al (2019) Repurposing drugs targeting the P2X7 receptor to limit hyperinflammation and disease during influenza virus infection. *Br J Pharmacol*; 176(19):3834-44.

Shi CS, Nabar NR, Huang NN, et al (2019) SARS-Coronavirus Open Reading Frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. *Cell Death Discov*; 5:101.

Siu KL, Yuen KS, Castano-Rodriguez C, et al (2019) Severe acute respiratory syndrome coronavirus ORF3a protein activates the NLRP3 inflammasome by promoting TRAF3-dependent ubiquitination of ASC. *FASEB J*; 33(8):8865-77.

Stout-Delgado HW, Cho SJ, Chu SG, et al (2016) Age-dependent susceptibility to pulmonary fibrosis is associated with NLRP3 inflammasome activation. *Am J Respir Cell Mol Biol*; 55(2):252-63.

Tate MD, Ong JDH, Dowling JK, et al (2016) Reassessing the role of the NLRP3 inflammasome during pathogenic influenza A virus infection via temporal inhibition. *Sci Rep*; 6:27912.

Vanden Berghe T, Demon D, Bogaert P, et al (2014) Simultaneous targeting of IL-1 and IL-18 is required for protection against inflammatory and septic shock. *Am J Respir Crit Care Med*; 189(3):282-91.

Commercially Confidential Information

Wang D, Hu B, Hu C, et al (2020) Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus-infected pneumonia in Wuhan, China. *JAMA*. doi: 10.1001/jama.2020.1585. [Epub ahead of print].

WHO (2020) COVID-19 Therapeutic Trial Synopsis. Geneva, Switzerland: WHO R&D Blueprint, Feb 18 2020.

Yang M, Lu L, Kang Z, et al (2019) Overexpressed CD39 mitigates sepsis induced kidney epithelial cell injury via suppressing the activation of NLR family pyrin domain containing 3. *Int J Mol Med*; 44(5):1707-18.

Yang X, Yu Y, Xu J, et al (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. doi: 10.1016/S2213-2600(20)30079-5. [Epub ahead of print].

Youm YH, Grant RW, McCabe LR, et al (2013) Canonical Nlrp3 inflammasome links systemic low-grade inflammation to functional decline in aging. *Cell Metab*; 18(4):519-32.

Yue Y, Nabar NR, Shi CS, et al (2018) SARS-Coronavirus Open Reading Frame-3a drives multimodal necrotic cell death. *Cell Death Dis*; 9(9):904.

Zhang LM, Zhang Y, Fei C, et al (2019) Neutralization of IL-18 by IL-18 binding protein ameliorates bleomycin-induced pulmonary fibrosis via inhibition of epithelial-mesenchymal transition. *Biochem Biophys Res Commun*; 508(2):660-6.

Zhang Y, Li J, Zhan Y, et al (2004) Analysis of serum cytokines in patients with severe acute respiratory syndrome. *Infect Immun*; 72(8):4410-5.

Zhou F, Yu T, Du R, et al (2020a) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*; 395(10229):1054-62.

Zhou P, Yang XL, Wang XG, et al (2020b) A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*; 579(7798):270-3.

16 Appendices

16.1 Appendix 1: 9-point ordinal scale determination

The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded. i.e. on Day 3, Day 2 score is obtained and recorded as Day 2. The scale is as follows:

Table 16-1 9-point 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

Source: [WHO \(2020\)](#)

16.2 Appendix 2: Liver event and laboratory trigger definitions and follow-up requirements

Table 16-2 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers	<ul style="list-style-type: none"> ALT or AST > 5 × ULN
If ALT, AST and total bilirubin normal at baseline:	<ul style="list-style-type: none"> ALP > 2 × ULN (in the absence of known bone pathology) TBL > 3 × ULN (in the absence of known Gilbert syndrome) ALT or AST > 3 × ULN and INR > 1.5 Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) Any clinical event of jaundice (or equivalent term) ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline:	<ul style="list-style-type: none"> ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms
ULN: upper limit of normal

Commercially Confidential Information

Table 16-3 Follow up requirements for liver laboratory triggers

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated), ALT or AST		
>1.5 – 3.0 ULN	<ul style="list-style-type: none"> Repeat LFTs within 48-72 hours 	Monitor LFTs weekly until resolution ^c to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	<ul style="list-style-type: none"> Repeat LFT within 48-72 hours Establish causality Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF 	Monitor LFTs weekly until resolution ^c to ≤ Grade 1 or to baseline (ALT, AST, TBL, ALB, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	<ul style="list-style-type: none"> Discontinue DFV890 Establish causality Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF 	ALT, AST, TBL, ALB, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	<ul style="list-style-type: none"> Hospitalization if clinically appropriate Establish causality Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF 	Investigator discretion

^aElevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

^b(General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

^cResolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator’s discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist’s consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Appendix 3: Severity of disease classification systems

Table 16-4 APACHE II

	Variable	Unit
	Age	years
	Glasgow Coma Score	
Vitals	Body temperature	°C
	Mean arterial pressure (MAP)	mmHg
	Heart rate	Beats per minute (bpm)
	Respiratory rate	breaths/m
Oxygenation	FiO ₂	%
	PaO ₂	mmHg
	Arterial pH	
	PaCO ₂	mmHg
	Altitude of site	Meters above sea level
Chemistry	Sodium	mEq/L
	Potassium	mEq/L
	Creatinine	mg/dL
	Acute Renal Failure	Yes/No
Hematology	Hematocrit	%
	White blood cell (WBC) count	x10 ⁹ /L
	Severe organ system insufficiency or is immunocompromised	Yes/No

Source: [Knaus et al \(1985\)](#)

Commercially Confidential Information

Commercially Confidential Information

16.4 Appendix 4: Severity of hepatic impairment (Child-Pugh)

Table 16-7 Child-Pugh scores and classification

	Points scored for observed findings		
	1 point	2 points	3 points
Encephalopathy grade*	Absent	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin($\mu\text{mol/L}$)	<34.2	34.2 – 51.3	>51.3
Serum albumin (g/L)	>35	28 – 35	<28
Prothrombin time (INR)	<1.16	1.16 – 1.56	>1.56
	Classification		
Child-Pugh grade	Child-Pugh A	Child-Pugh B	Child-Pugh C
Points required	5 – 6	7 – 9	10 – 15

*Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
 Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
 Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
 Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
 Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Source: [FDA \(2003\)](#)