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MAS825

CMAS825F12201 / NCT04382651

A Phase 2, randomized, placebo-controlled, participant and investigator blinded, multi-center study to assess efficacy and safety of MAS825 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function

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List of abbreviations

AE	Adverse Event
AIDS	Acquired immune deficiency syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AKI	Acute Kidney Injury
ANCOVA	Analysis of covariance
APACHE II	Acute Physiology and Chronic Health Evaluation II
APTT	Activated Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Classification
AUC	Area Under the Curve
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CIs	Confidence Intervals
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMO&PS	Chief Medical Office and Patient Safety
COVID-19	Coronavirus Disease 2019
CPAP	Continuous positive airway pressure
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical study report
CT scan	Computed Tomography Scan
CTC	Common Terminology Criteria
CV	coefficient of variation
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
dL	deciliter
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DQF	Data Query Form
DMC	Data Monitoring Committee
eATP	Extracellular adenosine triphosphate
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation

eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EOI	End of Infusion
eSAE	Electronic Serious Adverse Event
FAS	Full Analysis Set
FIH	First-in-human
FiO_2	Fraction of inspired oxygen
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
h	Hour
HA	Health Authority
HDL	High Density Lipoprotein
HBsAg	Hepatitis B surface antigen
HV(s)	Healthy Volunteers
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IEC	Independent Ethics Committeee
IFN-g	Interferon Gamma
IL 1β	Interleukin 1 beta
IMM	Inflammatory monocyte macrophage
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
kg	kilogram
LDH	lactate dehydrogenase
LDL	Low density lipoprotein
LFT	Liver function test
LLN	lower limit of normal

m	Meter
M^2	Squared meter

MedDRA	Medical dictionary for regulatory activities
min	minute
mg	milligram(s)
mL	milliliter(s)
mm^3	Cubic millimeter
mmHg	Millimeters Mercury
MR scan	Magnetic Resonance Scan
Nab	Neutralizing antibody
NK cells	Natural Killer cells
pM	picomolar
PA	posteroanterior
PaO_2	Partial Pressures of Oxygen
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PEF	Peak Expiratory Flow
PerfO	Performance Outcomes
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PoC	Proof of Concept
PoM	Proof of Mechanism
PPD	Premature Participant Discontinuation
PPT	Partial Prothrombin time
PR	Pulse Rate
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell(s)
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
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SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic Blood Pressure
sCR	serum creatinine
SD	standard deviation
SMQ	Standardized MedDRA Query
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SoC	Standard of Care
SpO2	Peripheral oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
TD	Study Treatment Discontinuation
TLR	Toll Like Receptors
TNF alpha	Tumor Necrosis Factor alpha

ULN	upper limit of normal
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WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of Child Bearing Potential

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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
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 case report forms (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
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
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.
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

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Protocol summary

Protocol number	CMAS825F12201
Full Title	A Phase 2, randomized, placebo-controlled, participant and investigator blinded, multi-center study to assess efficacy and safety of MAS825 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function
Brief title	Study of efficacy and safety of MAS825 in patients with COVID-19
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 MAS825 in addition to current standard of care (SoC) compared with placebo and SoC in controlling the inflammatory syndrome and resultant acute respiratory distress syndrome (ARDS) in hospitalized patients presenting with COVID-19 pneumonia and impaired respiratory function. Severe COVID-19 patients develop ARDS due to a hyperinflammatory syndrome that is characterized by pro-inflammatory cytokine release and cell death, resulting in severe pulmonary damage and dysfunction requiring mechanical ventilation. Specifically, patients with severe COVID-19 and respiratory failure have grossly elevated levels of IL-1β and its downstream cytokine IL-6, as well as IFN-g and IP-10 (CXCL10), both downstream markers of IL-18 pathway activation. MAS825 is expected to neutralize all inflammasome-dependent and independent-sources of IL-1β and IL-18 to arrest the autoinflammatory response, limiting further alveolar damage and improving clinical outcomes. Commercially Confidential Information
Primary Objective(s)	To evaluate the effect of MAS825, compared with placebo, on the Acute Physiology and Chronic Health Evaluation II (APACHE II) score
Secondary Objectives	The secondary objectives of this study are: • To evaluate the effect of MAS825, compared with placebo, on inflammatory status • To evaluate the effect of MAS825, compared with placebo, on clinical status • To evaluate the safety of MAS825, compared with placebo

Study design	This is a Phase 2, randomized, placebo -controlled, participant and investigator blinded, multi-center study to assess efficacy and safety of MAS825 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function. The study consists of five parts: 1. **Screening / Baseline / Treatment (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. Baseline blood tests will be performed in all patients; those who screen fail because of study inclusion / exclusion criteria (e.g., serum CRP, liver function tests), will not undergo randomization. Eligible patients will receive a single i.v. infusion of CCI MAS825 or placebo on Day -1 to 1. 2. **Treatment period (Day 2-15)**: Study assessments to be conducted every 2 days for hospitalized patients. If patients 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 and patient should return to the site for the Day 15 assessment (all other visits between discharge and Day 15 can be omitted). If 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). In case home nursing is not possible, patients will be contacted by phone on day 15. 3. **Follow-up (Day 16-29)**: After completion of the treatment period, patients will be observed until Day 29 or discharged from hospital, whichever is sooner. Study assessments to be conducted every 2 days for domiciled patients. Where patients 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. **Safety follow-up visit assessment (Day 45)**: A follow-up visit will be conducted at Day 45 if the patient is hospitalized. If patients are discharged from hospital prior to Day 45, a study visit will be conducted by telephone on Day 45. 5. **End of Study/Safety follow-up visit assessment (Day 127)**: A follow-up visit for safety will be conducted at Day 127 if the patient is hospitalized. If patients are discharged from hospital prior to Day 127, a study visit will be conducted by telephone on Day 127.
Study population	Approximately 120 male and female patients aged 18 years and above . 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.

Key Inclusion criteria	Participants eligible for inclusion in this study must meet all of the following criteria: 1. Male and female patients aged ≥18 years 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) 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) 5. Impaired respiratory function, defined as peripheral oxygen saturation (SpO_2) ≤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 or ferritin level ≥600 µg/L at screening 8. Body weight between 45 kg and 145 kg, inclusive, at screening 9. Ability to comply with the study protocol, in the investigator's judgment
Key Exclusion criteria	1. History of hypersensitivity to the investigational treatment or their excipients or to drugs of similar chemical classes 2. Suspected active or chronic bacterial (including Mycobacterium tuberculosis), fungal, viral, or other infection with the exception of 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 6.2.1.1, with the exception of anti-viral therapies orcorticosteroids • 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 Concomitant therapy) 7. Serum alanine transaminase (ALT) or aspartate transaminase (AST) >5 times upper limit of normal detected within 24 hours at screening/baseline (according to local laboratory reference ranges) or other evidence of severe hepatic impairment (Child-Pugh Class C, see Appendix 5)

	8. Absolute peripheral blood neutrophil count of ≤1000/mm^3 9. Estimated GFR (eGFR) ≤30 mL/min/1.73m^2 (based on CKD-EPI formula) 10. Pregnant or breastfeeding, or positive urine or serum pregnancy test in a pre-dose examination 11. 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 12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they agree to abstain from any sexual intercourse for a total of 29 days after randomization (the 14-day treatment period plus a 14-day follow-up period). 13. Current participation in any other investigational trials, with the exception of (not yet) approved COVID-19 therapies that are considered (local) standard of care (also see Section 6.2.1.1. for Prohibited drugs).
Study treatment	Patients will receive a single dose of MAS825 CCI i.v. in addition to Standard of Care, or placebo in addition to Standard of Care
Treatment of interest	The randomized treatment (the investigational treatment MAS825 in addition to SoC or control treatment of SoC alone)

Efficacy assessments	• 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 2):
	  • 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 and ferritin

Pharmacodynamic assessments	The pharmacodynamic objective for this study is to characterize the pharmacodynamic effects of MAS825 in patients with COVID-19 pneumonia via longitudinal measures of a number of analytes relative to baseline including the following: • CRP, ferritin, LDH, absolute whole blood neutrophil count, D-dimer, troponin

Key safety assessments	• Incidence and severity of adverse events / serious 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
Other assessments	Commercially Confidential Information
Data analysis	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. 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. All listings and tables will be presented by treatment group.
Key words	COVID-19, pneumonia, SARS-Cov2, APACHE II, MAS825, inflammasome

1 Introduction

1.1 Background

As of April 16, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been confirmed in over 2 Million people worldwide, with over 137,000 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 2020).

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 Rationale for targeting the inflammasome effector cytokines in patients with COVID-19 pneumonia and impaired respiratory function.

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-1β and IL-18. At low levels during initial stages of the disease, these cytokines amplify the innate immune response against viruses and promote the development of adaptive immune responses against the viruses (Tate et al 2016), 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-1β 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 (TNFα) (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).

Tissue damage may also result in NLRP3-independent release of IL-1β and IL-18 and the inactive pro-forms of these cytokines may be cleaved into the mature bio-active forms not only by caspase-1 but also by other proteases present in situ, such as neutrophil-derived elastases, mast cell derived chymases, and T cell- and NK cell-derived granzyme B (Afonina et al 2015). 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-1β 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 Excessive 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 extracellular ATP (eATP) release. eATP is sensed by the purinergic receptor P2X7 leading to potent NLPR3 inflammasome activation (Eckle et al 2007, Matsuyama et al 2008, Kuipers et al 2012, Liu et al 2019, Lv et al 2018, Wu et al 2013, Hasan et al 2017, Liu et al 2019, Lv et al 2018, Wu et al 2013, Hasan et al 2017). 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 (reviewed in 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).

1.1.3 Translational evidence that IL1β and IL-18 are pivotal to lung pathology in COVID-19 patients

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-1β (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-1β in the lungs is supported by findings in rat that transient lung expression of IL-1β 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 Th1 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.

1.1.4 Summary

The inflammasome and the pivotal mediators IL-1β, IL-18 and NLPR3 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 bispecific anti-IL-1/18 mAb (MAS825) 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 this treatment 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 when respiratory failure develops.

MAS825, a bispecific anti-IL-1β/IL-18 mAb rapidly neutralizes CCI of IL-1β and IL-18.

1.2 MAS825

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1.2.1 Nonclinical data

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1.2.2 Clinical data

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The overall preclinical and preliminary clinical, safety and laboratory assessments are is considered adequate to justify the continued development of MAS825 in patients with COVID-19 pneumonia and impaired respiratory function.

1.3 Purpose

The purpose of this study is to evaluate the efficacy and safety of MAS825 in addition to current standard of care (SoC) compared with placebo and SoC in controlling the inflammatory syndrome and resultant ARDS in hospitalized patients presenting with COVID-19 pneumonia and impaired respiratory function.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the effect of MAS825, compared with placebo, on the Acute Physiology and Chronic Health Evaluation II (APACHE II) score	• 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)**
• To evaluate the effect of MAS825, compared with placebo on inflammatory status	• Serum C-reactive protein (CRP) levels and ferritin

Objective(s)	Endpoint(s)
• To evaluate the effect of MAS825, compared with placebo, on clinical status	Endpoints based on the 9-point ordinal scale (Appendix 2): • 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
• To evaluate the safety of MAS825, compared with placebo	• Number of participants with Adverse Events (AE), Serious Adverse Events (SAE), clinically significant changes in laboratory measures, and vital signs

2.1 Primary estimands

The primary clinical question of interest is: What is the effect of MAS825 compared with placebo 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 treatment discontinuation?

The justification for the primary estimand is that it will capture the combined effect of the study drug in patients 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. Patients who die on Day 15 or earlier will be assigned the highest APACHE II score by any of the patients at any time during the trial. Note this imputation takes precedence over the APACHE II score on day of discharge.
3. Treatment of interest: the randomized treatment (the investigational treatment of MAS825 or placebo)
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.

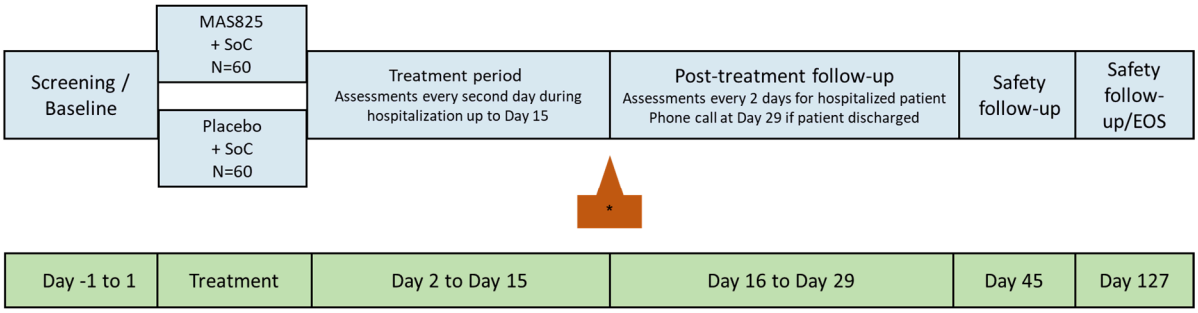
2.2 Secondary estimands

Not applicable

3 Study design

This is a Phase 2, randomized, placebo -controlled, participant and investigator blinded, multi-center study to assess the efficacy and safety of MAS825 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function (Figure 3-1).

Figure 3-1 Study design



* End points calculated on day of discharge in patients discharged prior to Day 15

The study consists of five parts:

1. **Screening / Baseline** / **Treatment** (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. Baseline blood tests will be performed in all patients; those who screen fail because of study inclusion / exclusion criteria (e.g., serum CRP, liver function tests), will not undergo randomization.

   Eligible patients will receive a single i.v. infusion of CCI MAS825 or placebo on Day -1 to 1 and will be observed until Day 15. Patients will be randomized as soon as possible, but within a maximum of 24 hours after screening in a 1:1 ratio to receive either treatment with MAS825 or placebo in addition to SoC. Randomization will be stratified according to the following, all of which may influence outcome in COVID-19:

   - age (≤65years, >65years)
   - administration of any anti-viral therapy (e.g., hydroxychloroquine, chloroquine, convalescent plasma, remdesivir, faripivavir, ritonavir, lopinavir) as SoC (yes / no)
   - presence of ≥1 of the following comorbidities: diabetes, hypertension, cardiovascular disease, chronic lung disease (yes / no)

2. **Treatment period** (Day 2-15): Study assessments to be conducted every 2 days for hospitalized patients. If patients 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 and patient should return to the site for the Day 15 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). In case home nursing is not possible, patients will be contacted by phone on day 15.

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

   If patients 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. **Safety follow-up visit assessment** (Day 45): A follow-up visit will be conducted at Day 45 if the patient is hospitalized. If patients are discharged from hospital prior to Day 45, a study visit will be conducted by telephone on Day 45.
5. **End of Study/Safety follow-up visit assessment** (Day 127): A follow-up visit for safety will be conducted at Day 127 if the patient is hospitalized. If patients are discharged from hospital prior to Day 127, a study visit will be conducted by telephone on Day 127.

4 Rationale

4.1 Rationale for study design

This is a randomized, placebo-controlled, participant- and investigator-blinded, multicenter study in hospitalized adult patients (≥18 years) with COVID-19-associated pneumonia and impaired respiratory function. This design supports the assessment of preliminary efficacy and as well as proof of concept and safety of MAS825 in addition to SoC in this critically ill patient population.

The **Screening / Baseline/Treatment 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** patients will be randomized in a 1:1 ratio to receive either treatment with MAS825 CCI i.v infusion or matching placebo in addition to SoC. Randomization is justified as there is at present no clinical evidence that MAS825 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. Stratification of randomization for age (≤65 years, >65 years), administration of any anti-viral therapy (yes / no) and presence of comorbidities (yes / no) is justified as these factors may influence outcome in COVID-19 patients and we wish to ensure equal distribution of these variables between the two study arms.

The **Study Endpoints** measure clinical status, clinical and in-hospital outcomes, and laboratory values, including serum CRP, a key biomarker of inflammasome inhibition and safety during and after the 14-day treatment period. These measurements are consistent with endpoints and measurement times for other studies of therapies for COVID-19.

The **Study Follow-up period** rationale is described in rationale for dose/regimen, duration of treatment and follow-up (Section 4.4)

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 is based on limitations in the available drug supply at this point in time. The current drug supply for MAS825 allow a maximum of 60 participants to be treated.

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 access 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 patients in this study.

To establish clinical efficacy based on APACHE II score, a sample size of 60 patients per treatment group provides 80% power when testing on an 10% 1-sided alpha level under the assumption that MAS825 in addition to SoC reduces the APACHE II score by 3.6 points more than placebo in addition to SoC (assumed standard deviation of 9.2 based on Yang et al 2020).

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Other clinical endpoints such as those derived from the 9-point ordinal scale were considered as primary endpoints. However, since these endpoints were binary in nature, the sample sizes required to have sufficient power to show statistically significant differences were much higher than those feasible with the limited available drug supply.

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 corticosteroids, though there is considerable inter-center variability regarding the use of these. Local SoC is permitted in all patients participating in the study, though every effort will be made by investigators to standardize this within individual centers.

Randomization for this study stratifies for the administration of antiviral therapy e.g., hydroxychloroquine, chloroquine, remdesivir, faripivavir, ritonavir, lopinavir, to ensure that treated and untreated patients are evenly distributed between the two treatment arms.

4.4 Rationale for dose/regimen, duration of treatment and follow-up

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Similarly, the efficacious dose of MAS825 to neutralize IL-1β has been estimated from IL-1β measurements in COVID-19 patients Commercially Confidential Information with pneumonia and respiratory failure (Huang et al 2020). The MAS825 dose level CCI for the study is further justified by;

- The dose will lead to rapid and simultaneous neutralization of all systemic free IL-I8 and IL-1β.
- This dose enables the treatment of severe COVID-19 where hyper-elevated levels of IL-1β and IL-18 is expected

- The dose of MAS825 has been administered to heathy volunteers with no identified safety concerns

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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), justifying treatment period selected.

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4.5 Purpose and timing of interim analyses/design adaptations

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4.6 Risks and benefits

4.6.1 Potential benefits and risks to study participants

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Clinically, there is evidence of efficiency with blockade of the downstream inflammasome pathway cytokine IL-6 (tocilizumab) in patients with cytokine release syndrome in the context of CAR-T therapy and some evidence from case reports in COVID-19 patients with a placebo-controlled Phase III clinical trial recently initiated (Zhang et al 2020, Mehta et al 2020, Ascierto et al 2020, NCT04320615).

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However, neither MAS825 nor other selective inhibitors of IL-1 and/or IL-18 have previously been studied in patients with COVID-19 pneumonia. Therefore, it remains currently unknown as to whether there will be a benefit for patients being treated with MAS825 in this disease.

The patients 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.

4.6.2 Potential risks to study 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.

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4.6.2.1 Potential risk of Infection

As with any immune-modulating compound, there is a theoretical risk of immune system impairment which might increase risk of infection in treated patients. However, MAS825 is not expected to elicit broad immune suppression, rather selectively neutralize the pro inflammatory IL-1β and free/bioactive IL-18 that are extremely elevated in COVID-19 patients, with simultaneous neutralization of both cytokines limited to the duration of the proposed post-study follow up. To mitigate potential risks of immune modulation and infection in this study, exclusion criteria include other immune suppressive treatments administered proximal to randomization, or concurrent use thereof. Patients are also excluded with known or suspected immunodeficiency state or evidence of active, serious bacterial, fungal or viral infections (other than SARS-CoV2).

4.6.2.2 Potential risk of acute infusion and/or hypersensitivity reactions

As with most biologic compounds, administration of MAS825 carries the risk of anaphylaxis and/or hypersensitivity-type reactions (see Section 16.1). MAS825 is administered as infusion over CCI to allow investigators discontinue treatment. In the event of such a reaction, Investigators should consider study-specific criteria for treatment discontinuation (Section 9.1.1); and the patient should be treated with supportive care.

Recommendations regarding evaluation and treatment of adverse events are provided in Section 6.6.2 and IB section 7.

4.6.2.3 Potential risk to women of child-bearing potential

At this stage of development, MAS825 has not yet been assessed in reproductive toxicology studies, and all women of childbearing potential (WOCBP) must be informed that exposure to MAS825 may involve unknown risks to the fetus if pregnancy were to occur.

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4.7 Overall risk benefit

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Therefore, the risks to COVID-19 patients 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 and periodic review of safety data by an independent DMC.

4.8 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 127 days, from each participant as part of the study. Approximately 190 mL blood will be collected over the first 15 days during which patients are hospitalized. For hospitalization of 29 days a total blood volume of approximately 250 mL will be collected. If safety follow-up visits occur at Day 45 and Day 127, an additional 25 ml of blood 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).

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See the Section 8.5.6.1 on the potential use of residual samples.

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 years 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)
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)
5. Impaired respiratory function, defined as peripheral oxygen saturation (SpO_2) ≤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 or ferritin level ≥600 µg/L at screening
8. Body weight between 45 kg and 145 kg, inclusive, 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.

1. History of hypersensitivity to the investigational treatment or their excipients or to drugs of similar chemical classes
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 6.2.1.1), with the exception of anti-viral therapies 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 Concomitant therapy)
7. Serum alanine transaminase (ALT) or aspartate transaminase (AST) >5 times upper limit of normal detected within 24 hours at screening/baseline (according to local laboratory reference ranges) or other evidence of severe hepatic impairment (Child-Pugh Class C, see Appendix 5)
8. Absolute peripheral blood neutrophil count of ≤1000/mm^3
9. Estimated GFR (eGFR) ≤30 mL/min/1.73m^2 (based on CKD-EPI formula)
10. Pregnant or breastfeeding, or positive urine or serum pregnancy test in a pre-dose examination

11. 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
12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they agree to abstain from any sexual intercourse for a total of 29 days after randomization (the 14-day treatment period plus a 14-day follow-up period). During the safety follow up (from day 29 onwards), WOCBP should practice highly effective contraception for 4 months following treatment with MAS825, when it is predicted that IL-18 and IL-1β will not be neutralized by MAS825.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to randomization. In the case of oophorectomy alone, only when the reproductive status of the women has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
13. Current participation in any other investigational trials, with the exception of (not yet) approved COVID-19 therapies that are considered (local) standard of care (also see Section 6.2.1.1. for Prohibited drugs).

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for prescribing/dispensing, and administering study treatment are outlined in the pharmacy manual.

6.1.1 Investigational and control drugs

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The investigational drug, MAS825 and the matching placebo will be prepared by Novartis and supplied as open labeled bulk medication to the unblinded site pharmacist (Table 6-1). An unblinded pharmacist or authorized designee is required to dispense the study drug.

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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)
MAS825 CCI	Commercially Confidential Information	Intravenous use	Commercially Confidential Information	

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Matching Placebo	Concentrate for solution for infusion	Intravenous use	Open label bulk supply; vials	Sponsor (global)

6.1.2 Additional study treatments

Patients assigned to the MAS825 arm will receive single dose of MAS825 CCI i.v. in addition to SoC, and patients assigned to the control arm will receive matching placebo in addition to SoC. Administered SoC in addition to study treatment will be supplied by the investigational site. No other investigational treatment beyond MAS825 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:

- MAS825 CCI i.v.
- Matching placebo i.v.

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 receiving MAS825 treatment.

During the course of the study and also prior to screening, participants may receive anti-viral therapies (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. prednisolone, dexamethasone, methylprednisolone), antibiotics, anti-coagulants and other agents/treatments where these form part of SoC for the treatment of COVID-19 at their participating center (per medical judgement).

Patients 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. Immunomodulatory (topical or inhaled) use for asthma and atopic dermatitis or corticosteroid use (per medical judgement) are not restricted.

Whilst the protocol defines experimental immunomodulatory treatments including but not limited to anti-IL-6 monoclonal antibodies as prohibited (Section 6.2.1.1), patients with significantly deteriorating clinical status after MAS825 or placebo 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. However, patients having received experimental immunomodulatory therapies as rescue therapy after treatment with MAS825 or placebo should remain in the study and the Investigator should continue collecting data on outcomes through the study visit schedule.

6.2.1.1 Prohibited drugs

The following medications are prohibited:

Experimental immunomodulatory therapies for the treatment of COVID-19, including, but not limited to canakinumab, anakinra and other anti-IL-1 antibodies, tocilizumab, sarilumab and other anti-IL-6 antibodies, ruxolitinib and other JAK inhibitors, eculizumab and other complement inhibitors (investigational or marketed).

Concomitant use of biologics including abatacept, rilonacept, rituximab and any other biologics (investigational or marketed) and TNF inhibitors including etanercept, adalimumab, infliximab and/or other TNF inhibitors (investigational or marketed).

All investigational medications being used in an investigational trial.

6.2.1.2 Permitted concomitant therapy requiring caution and/or action

Use of oral, injected or implanted hormonal methods of contraception are allowed while on MAS825.

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 informed consent form, 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 Interactive Response Technology (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.

Randomization will be stratified by:

- age (≤65years, >65years)
- administration of any anti-viral therapy (e.g., hydroxychloroquine, chloroquine, convalescent plasma, remdesivir, faripivavir, ritonavir, lopinavir) as SoC (yes / no)
- presence of ≥1 of the following comorbidities: diabetes, hypertension, cardiovascular disease, chronic lung disease (yes / no)

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

6.4 Treatment blinding

This is a blinded study. Participants and investigators will remain blinded to study treatment throughout the study, except where indicated below.

Participants, investigator staff, persons performing the assessments, and the clinical trial team (CTT) will remain blind to the identity of the treatment from the time of randomization until end of study visit applying the following rules:

- Randomization data are kept strictly confidential until the time of unblinding.
- Unblinding will occur in the case of participant emergencies and at the conclusion of the study.
- Unblinding of the CTT members may occur for the purpose of periodic review of the safety data.
- Unblinded results from the planned interim analysis after all participants have completed the Day 29 visit can be shared with the participants and site staff, if deemed appropriate.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site.

Drug product will be supplied in bulk, so an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist at the site will be notified by the IRT system that a participants randomized and to which treatment arm, which will then enable them to prepare the study drug. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor staff

The following unblinded sponsor roles are required for this study amend as appropriate:

- Unblinded field monitor(s)
- Unblinded clinical staff managing drug re-supply to site
- Unblinded sample analyst(s) CCI

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The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual participants.

Sponsor clinical staff are required to assist in the management and re-supply of investigational drug product. These individuals are not provided with randomization lists directly, but may be unblinded through communication of drug re-supply needs via the unblinded site pharmacists.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-2. For example, unblinded summaries and unblinded individual data can be shared with the team for all interim analyses.

Study programmers and other personnel involved in study data analysis CCI
are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing. The results from the planned interim analysis after all participants have completed their Day 29 visit (or discontinued from the study earlier) can be shared more broadly including with participants and site staff, if deemed appropriate. If this occurs, then all roles should be considered unblinded from this time points onwards. Otherwise, following final database lock all roles may be considered unblinded.

All unblinded personnel will otherwise keep randomization data or information that could unblind other study team members confidential and secure except as described above.

Table 6-2 Blinding and unblinding plan

	Time or Event			
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single participant unblinded)**	**Interim analysis**
Participants	B	B	UI	B*
Site staff	B	B	UI	B*
Unblinded site staff e.g. pharmacy staff (specify)	UI	UI	UI	UI
Global Clinical Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff e.g. for study treatment re-supply, unblinded monitor(s), sample analyst(s)	UI	UI	UI	UI
Unblinded Pharmacovigilance sponsor staff	UI	UI	UI	UI
Statistician/statistical programmer/ data analysts (e.g. CCI)	B	B	UI	UI
Independent committees used for assessing interim results, if required (e.g. DMC)	B	B	UI	UI
All other sponsor staff not identified above (i.e. trial team, project team, management & decision boards, support functions)	B	B	UI	UI

UI: Allowed to be unblinded on individual participant level

B: Remains blinded

NA: Not applicable to this study

* Unblinded results from the planned interim analysis after all subjects have completed their Day 29 visit (or discontinued earlier) can be shared with participants and site staff, if deemed appropriate. Results from any other interim analysis prior to the Day 29 visit should not be shared with participants and site staff.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

As dosing will be completed at the study site, assessment of compliance is not applicable. All study treatment administered will be recorded on the Study Treatment eCRF. Serum levels of MAS825 will be determined at pre-specified timepoints as measures of treatment compliance.

in all participants treated with MAS825, as detailed in "Assessment Schedule" in Table 8-1

6.6.2 Recommended treatment of adverse events

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

Treatment of infection

In the event of an infection, Investigators should consider early treatment with specific antimicrobial therapy based on clinical diagnosis or suspicion thereof (e.g., anti-viral treatment for herpes simplex or zoster) in consultation with infectious disease experts, as appropriate.

Treatment of acute infusion and/or hypersensitivity reactions

As with most biologic compounds, CCI administration of MAS825 carries the risk of anaphylaxis and/or hypersensitivity-type reactions (see Section 16.1). In the event of such a reaction, Investigators should consider study-specific criteria for treatment discontinuation (Section 9.1.1), and the patient should be treated with antihistamines and glucocorticoids. Depending on severity, subjects may also require supplemental oxygen, volume expansion, catecholamines and transfer to an intensive care setting. Plasmapheresis to decrease the systemic concentration of MAS825 may be considered dependent on the patient's condition. Subjects should be observed for at least four hours after resolution of signs and symptoms, and those who have experienced severe infusion reactions should be closely observed for 24 hours after resolution because of the risk for a biphasic episode.

Treatment of overdose

There is no clinical experience with MAS825 overdose. Should an overdose occur, the subject or patient should be carefully monitored for any potential symptoms, and if necessary, appropriate supportive care should be provided until the subject has recovered. The use of plasmapheresis may be considered to facilitate more rapid elimination of MAS825 from the peripheral circulation in the case of overdose.

At present there is insufficient information to provide specific recommendations regarding treatment of other potential adverse events (AEs) in this patient population. Acute kidney injury 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 adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency breaking of the assigned treatment code must only be undertaken when it is essential to treat the participant safely and efficaciously.

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- name (if available)
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

6.7 Preparation and dispensation

Each study site will be supplied with study drug and placebo in packaging as described under investigational and control drugs Section 6.1.1.

Details on preparation of study medication by unblinded pharmacist and dispensation are provided in Pharmacy Manual.

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 study treatment must be stored according to the instructions specified select as applicable 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 and comply with the legal requirements of each country. They will include storage conditions for the study 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 study 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.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study 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

Please refer to Pharmacy Manual.

Table 6-3 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
MAS825 CCI	CCI	Day 1 by i.v. infusion
Placebo		Day 1 by i.v. infusion

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), 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 informed consent form that complies with the ICH 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 Investigator's Brochure (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:

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- As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment
- Commercially Confidential Information
- As applicable, an optional Home Nursing visit consent for all participants to allow for home nursing visit if a site visit is not possible

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

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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 Day 15 visit should be performed, and if participant is prematurely discontinued at any visit after Day 15 and before Day 127, then assessments of Day 127 visit should be performed.

Table 8-1 Assessment schedule

Period	**Screening / Baseline / Treatment**	**Treatment[2]**								**Post-Treatment Follow-up**			**EOS**
Visit Name	**Screening / Baseline / Treatment[14]**	**Observation**							**Discharge[3]**	**Follow-up[4]** (if hospitalized assessments performed at site every 2 days; if discharged only telephone call on Day 29)		**Safety follow-up[4]**	**EOS/Safety Follow up[4]**
Days	**-1 to 1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**15**	**17, 19, 21, 23, 25, 27**	**29 (-1/+3 days)**	**45[5] (+/-7 days)**	**127 (+/- 7 days)[5]**
Domiciled (as required)	X	X	X	X	X	X	X	X	X	X	X		
CCI													
Inclusion / Exclusion criteria	X												
Demography	X												
Medical history/current medical conditions	X												
Presence SARS-CoV-2 virus / viral load[5]	X	CCI											
Chest X-ray (CXR), CT or MR scan per local SoC[5]	X								X[12]				
Randomization (IRT)	X												
Physical examination[13]	S	S							S		S	S	S
Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	Screening / Baseline / Treatment	Treatment[2]								Post-Treatment Follow-up			EOS
Visit Name	Screening / Baseline / Treatment[14]	Observation							Discharge[3]	Follow-up[4] (if hospitalized assessments performed at site every 2 days; if discharged only telephone call on Day 29)		Safety follow-up[4]	EOS/Safety Follow up[4]
Days	-1 to 1	2	4	6	8	10	12	14	15	17, 19, 21, 23, 25, 27	29 (-1/+3 days)	45[5] (+/-7 days)	127 (+/- 7 days)[5]
Respiratory status (spont. breathing, FiO_2, ventilator parameters, ECMO), fluid balance, need for CRRT	X	X	X	X	X	X	X	X	X	X	X	X	X
APACHE II, CCI	X	X	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	X	X
Weight and Height[7]	X				X				X				
ECG evaluation (local)[14]	X								X				
Pregnancy test – urine/serum (local lab)[9]	X								X				X
Blood chemistry including CRP, Ferritin, LDH, ANC, D-dimer, troponin and BNP (local lab)[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology (local lab)[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Commercially Confidential Information													
Drug administration record[11]	X												
Concomitant medications/Therapies including inotropic support	X												
Adverse events/serious adverse events	X												
Safety Follow up Call									X		X	X	X
Study completion information													X

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. Commercially Confidential Information
2. Study treatment may start immediately after obtaining the screening/baseline measurements and confirming eligibility. Day 15 visit should be performed for all patients.
3. If patient is discharged prior to Day 15 (early discharge), then assessments on the day of discharge should be performed according to the schedule listed under Day 15 and patient should return to the site for the Day 15 assessment, with a time window of +2 days (if hospital visit is not possible, then home nursing is allowed on day 15 (with a time window of +2 days) that should include all possible assessments including oxygen saturation with portable monitors). In case, home nursing is not possible, patients will be contacted by phone on day 15 (with a time window of +2 days), where respiratory history, performance status, adverse events, concomitant medication and medical and surgical history will be obtained). No time window for Day 15 is allowed if the patient is not discharged prior to day 15.

Period	Screening / Baseline / Treatment	Treatment[2]								Post-Treatment Follow-up			EOS
Visit Name	Screening / Baseline / Treatment[14]	Observation							Discharge[3]	Follow-up[4] (if hospitalized assessments performed at site every 2 days; if discharged only telephone call on Day 29)		Safety follow-up[4]	EOS/Safety Follow up[4]
Days	-1 to 1	2	4	6	8	10	12	14	15	17, 19, 21, 23, 25, 27	29 (-1/+3 days)	45[5] (+/-7 days)	127 (+/- 7 days)[5]

4. f patient is discharged after Day 15 and prior to Day 127 (discharge), then assessments on the day of discharge should be performed according to the schedule listed under Day 127. Furthermore, visits at Days 29, 45 and 127 should be conducted via phone for patients who were discharged prior to the visit (see footnote 3 for assessments to be obtained on the phone). Visits between day of discharge and Day 127 can be omitted. If the patient remains hospitalized, however, all assessments noted in the table should be conducted on the visit day noted.
5. 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.
6. Vital signs include heart rate, respiratory rate (if not on mechanical ventilation), systolic and diastolic blood pressure and body temperature. If possible, vital signs should be recorded at the same time at every visit for a patient (i.e. morning, afternoon or evening) and upon significant clinical changes. Oxygen saturation (if not on mechanical ventilation) or PaO_2/FiO_2 should be measured at the same time as the vital signs measurements.If patient is receiving supplemental oxygen (not on invasive ventilation) then oxygen flow rate and/or FiO2 and oxygen saturation to be collected.
7. If not possible to measure height, it can be reported by the patient. Height will be measured only at screening/baseline/treatment visit.
8. Hematology, blood chemistry and coagulation panel including CRP, Ferritin, LDH, ANC, D-dimer, troponin and BNP should be measured by the local laboratory.
9. Pregnancy test applicable only for females of childbearing potential; serum pregnancy test (serum hCG) will be performed by local laboratory. For enrollment a negative urine test is sufficient
10. Commercially Confidential Information
11. For the treatment day, all assessments should be performed pre-dose.
12. Chest X-ray, CT or MRI scan at Day 15 will be performed and reported only if available and performed according to SoC. The same method should be used at Day 15 (or on day of discharge if prior to Day 15) as was used at screening.
13. A complete physical examination will be performed at baseline. For the remaining time points, a targeted physical examination, as per investigator discretion, may be performed.
14. All procedures performed as part of local standard of care during this hospitalization, may be used for screening/baseline assessments provided that they were performed up to 24 hours prior to ICF signature. ECG examination conducted during this 24h window will be accepted as long as the same diagnostic method is used throughout the study.
15. Urine output to be measured as per local SoC.

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/ 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 informed consent form 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 and child-bearing potential (for females only).

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.

8.3.1 Vital signs and oxygen saturation and use

Vital sign measurements include respiratory rate, pulse rate, systolic and diastolic blood pressure, and body temperature. If possible, vital signs should be recorded at the same time at every visit for a patient (i.e. morning, afternoon or evening) and upon significant clinical changes.

Peripheral oxygen saturation on room air should also be measured at the same time as the vitals, if not on supplemental oxygen. If patient is receiving supplemental oxygen (not on invasive ventilation), then oxygen flow rate (L/min) and/or fraction of inspired oxygen (FiO_2) and oxygen saturation should be recorded. PaO_2/FiO_2 should be recorded as needed (see Appendix 5 for guidance on estimation of PaO2/FiO2).

8.3.2 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) (Appendix 4). The worst value for each parameter in the last 24 hours will be entered in the CRF, with parameters recorded, if possible, at the same time at every visit for a patient (i.e. morning, afternoon or evening) and upon significant clinical changes. 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 submission. The score will be recorded only for the screening/baseline visit in the CRF.

Mean arterial pressure (MAP) may either be directly measured or calculated from the diastolic and systolic blood pressure (per medical judgement).

For oxygenation variables, where patients have an arterial line sited an arterial blood sample should be used. In patients, without an arterial line sited should have either an arterial, or equivalent measurement (eg capillary blood gas). In the case, where an arterial sample is not indicated or feasible clinically, a venous blood gas sample scan be used and the PaO_2 estimated (per medical judgement, see Table 16-4 for guidance on estimation of PaO2). For a given patient the same methodology to obtain the APACHE II parameters should utilized throughout the study where clinically feasible/indicated.

8.3.3 Clinical status (9-point ordinal scale)

Assessment of clinical status using a 9-point ordinal scale (WHO 2020) will be recorded at baseline, Day 2 and then every other day until Day 29 for hospitalized patients (Appendix 2). If a patient is discharged from the hospital, the assessment will be made by phone on the visit dates noted in Table 8-1. Each day, the patient's status from the previous calendar day is reviewed; the ordinal score is assigned based on the patient's worst status from the previous day. This score (based on the review of the previous day) will be recorded (i.e. on Day 3, the Day 2 score is determined from review of all data recorded on Day 2, and the worst score is recorded as the score for Day 2). In addition, on Day 127 or the Day of discharge, clinical status on Day 127 or the Day of discharge should be recorded.

8.3.4 CRP and Ferritin

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

8.3.5 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.

For details on AE collection and reporting, refer to AE Section 10.1.1.

Assessment	Specification
Physical examination	A complete physical examination 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.
Vital signs	Vital signs will include the collection of rectal, otic or oral body temperature (recorded in °C), blood pressure (BP) and pulse measurements. 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.
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 patient will be entered in the CRF.

8.4.1 Laboratory evaluations

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

Safety laboratory evaluations will be performed by the local laboratory.

Special clinical laboratory evaluations

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab 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 (local)

Clinically notable laboratory findings are defined in Appendix 3.

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands
Chemistry	Albumin (ALB), Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, 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, Ferritin, D-dimer, Troponin, Brain Natriuretic Peptide (BNP)
Coagulation*	Prothrombin time (PT), International normalized ratio [INR]), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)
Pregnancy Test	Serum / Urine pregnancy test (refer to 'Pregnancy and assessments of fertility' Section 8.4.5)
*Coagulation assessment should include only those tests routinely performed according to local standard of care.	

8.4.2 Physical examination

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

8.4.3 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.

8.4.4 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 participant is at rest.

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

Single ECGs are to be collected with ECG machines available at the site. Single 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.

ECG examination conducted within the 24h time window prior to screening will be accepted as long as the same diagnostic method is used throughout the study.

Each ECG tracing must be labeled with study number, participant initials, participant number, 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.

8.4.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have urine or serum pregnancy testing at screening and Day 15 and Day 29 if hospitalized. Additional pregnancy testing might be performed if requested by local requirements. Pregnancy tests will be conducted at the local laboratory. If discharged from hospital, WOCBP should carry out a home pregnancy test on Day 15, Day 29, monthly thereafter until end of study, and should inform study site/investigator if they become pregnant.

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.

8.4.6 Other safety evaluations

Chest X-ray

A standard chest X-ray (CXR) or chest CT or MR scan, will be performed as per local standard practice to diagnose pneumonia; except for those who have had a valid test done within 5 days of randomization. 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 screening.

Additional assessments may be performed, as needed.

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

8.4.7 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 and therapeutic response in this setting.

8.5 Additional assessments

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9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

This study involves single i.v. infusion of an approximate duration of CCI , and therefore the infusion can be interrupted if necessary. In case the clinical setting requires it (e.g. long i.v. line),

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

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision - participants may choose to discontinue study treatment for any reason at any time. The investigator believes that continuation would negatively impact the safety of the participant or the risk/benefit ratio of trial participation
- Moderate or severe hypersensitivity reaction occurs, including any of the following: anaphylaxis (Section 16.1), fever, chills, urticaria, dyspnea, headache, myalgia, hypotension. Immediate discontinuation of study treatment and initiation of appropriate medical treatment is required in such cases.
- Moderate or severe infusion-related reaction to study drug.
- Any protocol deviation or situation that results in a significant risk to the participant's safety.

The appropriate personnel from the site and Novartis will assess whether investigational drug treatment should be discontinued for any participant whose treatment code has been broken inadvertently for any reason.

If discontinuation of study treatment occurs, investigator must determine the primary reason for the participant's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

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 'Withdrawal of Informed Consent' Section 9.1.2). Where possible, they should return for the assessments indicated in the Assessment Schedule. 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 'Lost to follow-up' 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.

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/Sponsor 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

An independent Data Monitoring Committee will regularly review study data, including mortality and SAEs. Enrollment in the study will be placed on hold if any of the following occurs:

- There is a mortality rate which is 25% greater in the MAS825 arm than in the placebo arm (assessed after the first 30, 60 and 90 participants are enrolled).
- The DMC or Sponsor consider that the number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justify putting the study on hold.

The study may resume following the safety review, if the Investigator and Sponsor agree it is safe to proceed

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (if applicable, insert additional study-specific criteria or modify the following criteria as per the study set up):

- 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 (provide instruction for contacting the participant, when the participant should stop taking drug, when the participant should come in for a final visit) 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).

Randomized and/or treated participants will have a follow-up visit or call conducted at Days 29, 45 & 127. 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:

   1. Dose not changed
   2. Dose Reduced/increased
   3. 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:

1) they induce clinical signs or symptoms
2) they are considered clinically significant
3) 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 conditions(s) which meets any one of the following criteria:

Article I. fatal

Article II. 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 Investigator's Brochure 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 than24 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 study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

The newborn will be followed up for a minimum of 1 month after delivery.

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.

Study 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 study 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 Section 10.1.1, Section 10.1.2 and 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 16-1 in Appendix 3 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-2 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 16-2. Repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP and G-GT) 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.
- 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

This study will include a Data Monitoring Committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The committee will include Novartis employees and at least one external medical expert. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC

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 Electronic Case Report Forms (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 (CRO)) 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 (ATC) 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 site's data. The field monitor will 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 study 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. 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 that have received any study drug.

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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 dates and times of MAS825 dosing 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 MAS825 compared with placebo on the APACHE II score. A decrease in the score is considered a favourable 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 evaluated 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 MAS825 vs placebo 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 MAS825 is not different to placebo 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 SAP.

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).

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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 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 MAS825 vs placebo will be reported with 90% CIs. The 1-sided p-value for the overall treatment factor will be reported. Ferritin levels will also be analyzed in the same manner.

12.5.2.5 Other safety evaluations

The proportion of participants who have a positive SARS-CoV-2 test will be summarized by treatment group and visit.

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12.6 Analysis of exploratory endpoints

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12.9 Sample size calculation

12.9.1 Primary endpoint(s)

The sample size is limited to maximum of 60 participants to be treated with a single i.v.dose of MAS825 due to limitations in the available drug supply at this point in time.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 MAS825 reduces the APACHE II score by 3.6 points more than placebo (assumed standard deviation of 9.2 based on Yang 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 a 1% 1-sided alpha level under the assumption that MAS825 reduces CRP by 44% more than placebo (assumed CV of 130% 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 Good Clinical Practice (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 Institutional Review Board/Independent Ethics Committee (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. In addition, after study completion (defined as last patient last visit) and finalization of the study report 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, 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 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 Health Authorities, 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

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16 Appendices

16.1 Appendix 1: Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from baseline.

16.2 Appendix 2: 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:

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)

16.3 Appendix 3: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 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 Total bilirubin > 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:	• 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

Table 16-2 Follow up requirements for liver laboratory triggers

Criteria	Actions required	Follow-up monitoring
Total Biliruin (isolated)		
>1.5 – 3.0 ULN	• 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)	• 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, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Establish causality • Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

[a]Elevated 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

[c]Resolution 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.

16.4 Appendix 4: ICU scores

Table 16-3 APACHE II

	Variable	Unit
	Age	years
	Glasgow Coma Score	
Vitals	Body temperature	^{o}C
	Mean arterial pressure (MAP)	mmHg
	Heart rate	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)

Table 16-4 Estimating PaO_2 from a given SpO_2

SpO_2 (%) PaO_2 (mmHg)	PaO_2 (mmHg)
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

Source : (Vincent et al 2009)

Table 16-5 Estimating FiO_2

Method	O_2 flow (l/min)	Estimated FiO_2 (%)*
Nasal cannula	1	24
	2	28
	3	32
	4	36
	5	40
	6	44
Nasopharyngeal catheter	4	40
	5	50
	6	60
Face mask	5	40
	6-7	50
	7-8	60
Face mask with reservoir	6	60
	7	70
	8	80
	9	90
	10	95

Source : (Vincent et al 2009)

* If patient is breathing air then estimated Fi02 is 21%

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Table 16-8 GLASGOW COMA SCORE

Eye Opening

Criterion	Rating	Score
Open before stimulus	Spontaneous	4
After spoken or shouted request	To sound	3
After finger tip stimulus	To pressure	2
No opening at any time, no interfering factor	None	1
Closed by local factor	Non testable	NT

Verbal Response

Criterion	Rating	Score
Correctly gives name, place and date	Orientated	5
Not orientated but communication coherently	Confused	4
Intelligible single words	Words	3
Only moans/groans	Sounds	2
No audible response, no interfering factor	None	1
Factor interfering with communication	Non testable	NT

Best motor response

Criterion	Rating	Score
Obey 2-part request	Obeys commands	6
Brings hand above clavicle to stimulus on head neck	Localising	5
Bends arm at elbow rapidly, but features not predominantly abnormal	Normal flexion	4
Bends arm at elbow, features clearly predominantly abnormal	Abnormal flexion	3
Extends arm at elbow	Extension	2
No movement in arms/legs, no interfering factor	None	1
Paralysed or other limiting factor	Non testable	NT

Source: (Teasdal and Jennett 1974)

16.5 Appendix 5: Severity of hepatic impairment (Child-Pugh)

	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(µmol/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)