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ACZ885/Canakinumab

Clinical Trial Protocol CACZ885D2310 / NCT04362813

Phase 3 multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of canakinumab on cytokine release syndrome in patients with COVID-19-induced pneumonia (CAN-COVID)

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List of abbreviations

AE	Adverse Event
ACE2	Angiotensin-converting enzyme 2
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
ARDS	Acute respiratory distress syndrome
AST	Aspartate Aminotransferase
ASTCT	American society for transplantation and cellular therapy
[redacted]	[redacted]
BUN	Blood Urea Nitrogen
CFR	Case fatality rate
CMO&PS	Chief Medical Office and Patient Safety
CoV	Coronaviruses
COVID-19	Coronavirus disease 2019
[redacted]	[redacted]
CRF	Case Report/Record Form (paper or electronic)
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT Scan	Computed tomography scan
DMC	Data Monitoring Committee
[redacted]	[redacted]
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic Data Capture
EMA	European medicines agency
EOI	End of Infusion
FAS	Full analysis set
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
hr	Hour
i.v./IV	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 Committee
IL	Interleukin
IL-1R	IL-1 receptor

[redacted]

IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to treat
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
PaO_2	Partial pressure of oxygen
PBO	Placebo
PCR	Polymerase chain reaction
[redacted]	[redacted]
[redacted]	[redacted]
RRT	Renal replacement therapy
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SOC	Standard of care
SpO_2	Peripheral capillary oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	upper limit of normal
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
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.

[redacted]

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
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.
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

[redacted]

Amendment 1 (01-Jun-2020)

Amendment rationale

At the time of this amendment approximately 96 patients have been randomized and the study continues to screen patients.

This protocol amendment is primarily issued for the following reasons:

- A clarification on source data verification approaches was included to align with the EMA Guidance on the Management Of Clinical Trials During The COVID-19 (Coronavirus) Pandemic (Version 3, 28APR20).
- In addition, as requested by FDA, the inclusion criteria 2 was updated to allow patients ≥ 12 years of age to be included in the trial in the US only.

Changes to the protocol

Inclusion criteria 2 was updated to include patients ≥ 12 years of age in the US only and the informed consent procedure in inclusion criteria 4 was updated in line with this. The Protocol Summary and Section 3, Section 5, Section 5.1 and Section 7, were updated with text regarding the modified inclusion criteria 2 and 4.

Clarification that all investigational medications being used in an investigational trial are prohibited was added to Section 6.2.2.

Table 8-1 was updated to clarify that assessments/procedures performed 0–24 hours prior to randomization could be included for screening purposes. This clarification was aligned throughout the document. The footnote was also updated to add guidance [redacted] and when samples should be taken. The text "if arterial blood gas was measured" was removed as a condition for measuring PaO_2/FiO_2 and this is reflected in Section 8.3.2 also. Additional minor clarifications and editorial changes were made in the table.

Section 8.3.1 was updated to add clarification on the timing of assessing the 9-point ordinal scale during the study and on Day 29/discharge.

In Section 8.4.1.2, triglycerides was removed from the listed assessments in the chemistry panel, as these are not required.

[redacted]

Section 10.1.4 was updated to clarify the reporting of enrolled pregnant patients to Novartis.

A clarification on source data verification approaches was added to Section 11.3 to align with the EMA Guidance on the Management Of Clinical Trials During The COVID-19 (Coronavirus) Pandemic (Version 3, 28APR20).

[redacted]

[redacted]

Other minor edits have been made to further optimize the clinical trial protocol. Typographical errors have been corrected to increase clarity and consistency of the text.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

The changes herein do NOT affect the trial specific model ICF. The US-specific protocol change to include patient's ≥12 years of age in the trial requires the addition of parent/guardian consent and adolescent assent.

[redacted]

Protocol summary

Protocol number	CACZ885D2310
Full Title	Phase 3 multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of canakinumab on cytokine release syndrome in patients with COVID-19-induced pneumonia (CAN-COVID)
Brief title	Study of efficacy and safety of canakinumab treatment for CRS in participants with COVID-19-induced pneumonia
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the efficacy and safety of canakinumab for the treatment of cytokine release syndrome (CRS) in patients with COVID-19-induced pneumonia. As of March 28, 2020, coronavirus disease 2019 (COVID-19) has been confirmed in 629,355 people worldwide. The mortality rate has been reported to be approximately 3.7%, compared with a mortality rate of less than 1% from influenza (Mehta et al 2020). There is an urgent need for effective treatment. Accumulating evidence suggests that patients develop severe acute pneumonia due to COVID-19 with cytokine release syndrome (CRS). Currently, there is no clinical experience with canakinumab in the treatment of CRS, pneumonia or SARS-CoV-2 infection. However, the cytokine profiling of patients with severe COVID-19 that includes elevated levels of interleukin (IL)-2, IL-7, IL-6, IL-1, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, tumor necrosis factor-α and other pro-inflammatory cytokines suggests that canakinumab could improve patient outcomes (Mehta et al 2020; Zhou et al 2020).
Primary Objective	To demonstrate the benefit of canakinumab + SOC in increasing the chance of survival without ever requiring invasive mechanical ventilation among patients with COVID-19-induced pneumonia and CRS
Secondary Objectives	• To demonstrate the benefit of canakinumab in reducing 4-week case fatality rate (CFR) among patients with COVID-19-induced pneumonia and CRS regardless of other subsequent clinical interventions • To evaluate change from baseline in clinical serologic measurements related to CRS in COVID-19 patients with pneumonia • To evaluate safety of canakinumab in patients with COVID-19-induced pneumonia and CRS
Study design	This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of canakinumab in patients with COVID-19-induced pneumonia and CRS. The study will enroll patients to canakinumab or placebo, in addition to standard of care per local practice, which may include anti-viral treatment, corticosteroids and/or supportive care. The total trial duration will be 126 days after the canakinumab or placebo dose. Safety will be closely monitored with an internal Novartis DMC during the study.

[redacted]

Study population	Approximately 450 patients with diagnosed COVID-19-induced pneumonia and CRS will be randomized to canakinumab or placebo in a 1:1 ratio
Key Inclusion criteria	1. Male or female 2. Adults ≥ 18 years old (for US only: patients ≥ 12 years old) 3. Body weight ≥40 kg 4. Informed consent must be obtained prior to participation in this study. For US patients 12 - < 18 years old; parent/guardian consent must be obtained and assent if applicable. 5. Clinically diagnosed with SARS-CoV-2 virus by PCR or by other approved diagnostic methodology within 7 days prior to randomization 6. Hospitalized with COVID-19-induced pneumonia evidenced by chest x-ray or CT scan (taken within 5 days prior to randomization) with pulmonary infiltrates 7. SpO_2 ≤ 93% on room air, or arterial oxygen partial pressure (PaO_2)/ fraction of inspired oxygen (FiO_2) < 300mmHg (1mmHg=0.133kPa) (corrective formulation should be used for higher altitude regions (over 1000m)) 8. C-reactive protein ≥20 mg/L or ferritin level ≥600 µg/L
Key Exclusion criteria	1. History of hypersensitivity to canakinumab or to biologic drugs 2. Intubated and on mechanical ventilation (invasive) at time of randomization 3. Treatment with immunomodulators or immunosuppressant drugs, including but not limited to tocilizumab, TNF inhibitors and anti-IL-17 agents within 5 half-lives or 30 days (whichever is longer) prior to randomization with the exception of anakinra which is excluded within 5 half-lives only. *Note: Immunomodulators (topical or inhaled) for asthma and atopic dermatitis and corticosteroids (any route of administration) are permitted* 4. Suspected or known untreated active bacterial, fungal, viral, or parasitic infection with the exception of COVID-19 5. Neutropenia with ANC <1000/mm^3 6. 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 7. In the opinion of the investigator, progression to death is imminent and highly likely within the next 24 hours, irrespective of the provision of treatments 8. Current participation in any other investigational trials
Study treatment	Arm 1: Canakinumab 450 mg for body weight 40-<60 kg, 600 mg for 60-80 kg, or 750 mg for >80 kg in 250 mL of 5% dextrose infused IV over 2 hours Arm 2: 250 mL of 5% dextrose infused IV over 2 hours Canakinumab or placebo infusions will be prepared and blinded by an unblinded pharmacist or designated staff member.
Treatment of interest	Randomized canakinumab or placebo as described above. In addition, all patients will receive SOC per local practice for the treatment of COVID-19-induced pneumonia. The SOC may include anti-viral treatment, corticosteroids and/or supportive care.

[redacted]

Efficacy assessments	The WHO 9-point ordinal scale of clinical status will be assessed on a daily basis at baseline and after study treatment during hospitalization as well as on Days 15, 29, 57 and 127 [redacted]
[redacted]	[redacted]
Key safety assessments	Adverse event monitoring, physical examinations, and monitoring of laboratory safety values.
Other assessments	[redacted]. Standard safety and laboratory assessment will be performed during hospital stay and outpatient visits after discharge from hospital (See Assessment Table). In addition, CRS / [redacted] • CRP • Ferritin [redacted] Additional Laboratory measurements: • Absolute neutrophil count • Monocytes • Lymphocytes • Lactate dehydrogenase • D-dimer levels
Data analysis	An absolute increase of 15% survival without ever requiring invasive mechanical ventilation is considered a clinically meaningful benefit. A total sample size of 450 with 1:1 randomization ratio is planned for the study, which is expected to ensure at least 89% power for the primary analysis. Conditional on the rejection of null hypothesis in primary analysis, and if the true 4-week case fatality rate for the control arm is no less than 15%, there will be at least 70% power to prove if canakinumab leads to a 50% relative reduction in the risk of death. The primary analysis will be performed after all patients complete Day 29 assessment or discontinue early from the study before Day 29. Final analysis will happen after all patients complete the study. The primary analysis follows a treatment policy strategy to estimate the difference and odds ratio between the response rates of canakinumab and control arms. Hypothesis testing will be performed based on the odds ratio estimated using a logistic regression model with study treatment, region and baseline

[redacted]

	clinical status as covariates. The two-sided type I error will be controlled at 0.05. Key secondary endpoint of 4-week case fatality rate (CFR) will be compared between the two treatment arms using a logistic regression model with study treatment, region and baseline clinical status as covariates. Using a hierarchical testing procedure for familywise 2-sided type I error control at 0.05, the hypothesis test in key secondary analysis will be performed if and only if the null hypothesis in the primary analysis is rejected. Other secondary analyses will include descriptive summaries without hypothesis testing. [redacted] Safety summaries will be produced for regular DMC safety monitoring.
Key words	COVID-19 pneumonia, SARS-CoV-2, canakinumab

[redacted]

1 Introduction

1.1 Background

Coronavirus disease 2019 (COVID-19) is a global pandemic (Gorbalenya et al 2020, WHO 2020a). What started as an epidemic of COVID-19 cases with unexplained lower respiratory tract infections first detected in Wuhan, the largest metropolitan area in China's Hubei province, and reported to the World Health Organization (WHO) Country Office in China on December 31, 2019 has now spread globally with 629,355 confirmed cases worldwide and 28,963 deaths reported (March 28, 2020; Worldometers 2020). As of March 12, 2020, the mortality rate was calculated at approximately 3.7%, compared with a mortality rate of less than 1% from influenza. Currently, there are no approved treatments nor vaccines, and so there is an urgent need for effective treatment (Mehta et al 2020).

COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and belongs to family coronoviridae (Ahn et al 2019, Gorbalenya et al 2020, WHO 2020a). Coronaviruses (CoV) are positive-stranded RNA viruses with a crown-like appearance under an electron microscope due to the presence of spike glycoproteins on the viral envelope. They are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as the severe acute respiratory syndrome coronavirus (SARS-CoV) from 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) from 2012 (MERS). Like SARS-CoV and MERS-CoV, it is believed that SARS-CoV-2 moved from bats to an intermediate host (possibly a Malayan Pangolin, which shares 91% nucleotide identity) and then to humans (Ahn et al 2019, Gorbalenya et al 2020).

Patients infected with SARS-CoV-2 present with a wide range of clinical severity varying from asymptomatic to a severe form of interstitial pneumonia, which may progress towards acute respiratory distress syndrome (ARDS) and/or multi organ failure and death. The clinical symptoms of COVID-19 patients include fever, cough, fatigue, loss of smell, and shortness of breath within 2-14 days after exposure (CDC 2020). SARS-CoV-2 uses the same receptor as SARS-CoV, angiotensin-converting enzyme 2 (ACE2) and mainly spreads through the respiratory tract (Hoffmann et al 2020, Xu H et al 2020, Zhao D et al 2020). Although currently, the pathogenesis of the pulmonary manifestations of COVID-19 remains poorly defined and knowledge of factors affecting disease severity is limited, underlying illnesses such as diabetes, cardiovascular diseases, hypertension, cancer and older age are associated with poorer outcome (Huang et al 2020, Chen et al 2020, Guan et al 2020). Cytokine profiling of patients with severe COVID-19 includes elevated levels of interleukin (IL)-2, IL-7, IL-6, IL-1, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α and tumor necrosis factor-α (Wang et al 2020, Mehta et al 2020, Wan et al 2020, Liu et al 2020, Zhou et al 2020, Diao et al 2020).

COVID-19 associated pneumonia and ARDS have raised questions about the possible role of a cytokine storm in pathogenesis of SARS-CoV-2. Profound lung injury, in particular that of type II alveolar epithelial cells that express the viral entry receptor, ACE2, has the potential to activate intracellular pathogen sensing platforms called inflammasomes (Chen et al 2019, Xu H et al 2020, Zhao and Zhao 2020). Activated inflammasomes initiate cleavage of pro-IL-1β to active IL-1β, resulting in a robust pro-inflammatory response with activation and subsequent recruitment of neutrophils and macrophages with the normal physiological role of controlling

[redacted]

viral infection (Bauernfeind et al 2011, Zhao and Zhao 2020). An overexuberant inflammatory response as the result of accumulation of innate immune cells results in vascular leakage, pulmonary edema, hypoxia culminating in ARDS (Leff et al 1994, Olman et al 2004, Ganter et al 2008). Furthermore, severe COVID-19 patients are reported to exhibit increased circulating levels of IL-1β and IL-6 that appears to negatively impact T cell numbers while also increasing the expression of checkpoint inhibitor programmed death 1 on T cells (Diao et al 2020, Zheng et al 2020). In contrast, non-severe patients that recover show decreased IL-6, IL-10 and interferon-γ in circulation, suggesting resolving inflammation and the recruitment of antibody-secreting B cells, T_{FH} cells and activated CD4+ and CD8+ T cells, together with IgM and IgG SARS-CoV-2-binding antibodies, in the patient's blood before the resolution of symptoms (Thevarajan et al 2020). This strongly suggests that lack of resolution of inflammation is a hallmark of severe COVID-19 patients and given that IL-1β is a key regulator of inflammation in a variety of chronic conditions such as cardiovascular disease, autoinflammatory diseases, and cancer (Toldo et al 2014, Fang et al 2018, Mantovani et al 2018), it strongly suggests a role of IL-1β in non-resolving inflammation following SARS-CoV-2 in severe COVID-19 patients with pneumonia and ARDS.

Numerous clinical and preclinical studies demonstrate that inflammasome-derived IL-1β plays a critical role in the development of sterile inflammation during ARDS and contributes to acute lung injury (Patton et al 1995, Kolb et al 2001, Ganter et al 2008). IL-1β is significantly elevated in bronchoalveolar fluid and plasma in patients with ARDS compared to healthy controls and is associated with poor clinical outcomes (Meduri et al 1995, Park et al 2001, Bouros et al 2005). Patients with ARDS following infection with other coronaviruses such as MERS-CoV and SARS-CoV exhibit a high IL-1β signature that includes downstream mediators, IL-6 and IL-8 (He et al 2007, Lau et al 2013, Min et al 2016, Alosaimi et al 2020), strongly indicating that inflammation-driven ARDS in severe COVID-19 patients might be driven by IL-1β.

The Spanish influenza pandemic of 1918 and seasonal outbreaks of influenza sub-strains have both been documented to cause ARDS in mice and primates with an acute pulmonary inflammatory response that includes neutrophils and macrophages and high levels of IL-1β in bronchoalveolar lavage and plasma (Meduri et al 1995, Park et al 2001, Beigel et al 2005, Bouros et al 2005, Tumpey et al 2005, Kobasa et al 2007, Perrone et al 2008). In mice that lack IL-1R, the AIM-2 inflammasome - the acute pathological granulocytic response - is markedly reduced, and attenuated lung injury and significant improvement in survival against influenza A viruses are observed, while viral burden in the lung is not altered (Schmitz et al 2005, Zhang et al 2017). Blockade of IL-1β either via administration of recombinant IL-1R antagonist or blocking antibody prevented an influenza-driven inflammatory response, reducing the development of pulmonary fibrosis and acute lung damage (Gasse et al 2007, Kim et al 2015). These data strongly indicate that IL-1β is a key cytokine orchestrating acute lung injury and inflammatory response (Kim et al 2015) contributing to ARDS following infection with respiratory viruses other than SARS-CoV-2.

CAR-T cell therapy is a highly specific and effective therapy for a subset of B cell malignancies (Porter et al 2015, Schuster et al 2017). However, broader use of this powerful approach is limited by potentially lethal toxicities, such as the induction of severe cytokine release syndrome (CRS) and neurotoxicity. Characteristics of CRS include fever, fatigue, headache, encephalopathy, hypotension, tachycardia, coagulopathy, nausea, capillary leak, and multi-

[redacted]

organ dysfunction (Porter et al 2018) and is graded using the ASTCT CRS grading criteria (Appendix 2). The reported incidence of CRS after CAR-T cell therapy ranges from 50% to 100%, with 13% to 48% of patients experiencing the severe or life-threatening form. Serum levels of inflammatory cytokines are elevated, particularly IL-6, and IL-6R blockade using tocilizumab has been approved for the treatment of severe or life-threatening CAR-T cell-induced CRS (Le et al 2018, Kotch et al 2019). Given the increased levels of IL-6 in COVID-19 patients and the role of IL-6 in SARS-associated ARDS (Wang et al 2020, Mehta et al 2020, Wan et al 2020, Liu et al 2020, Zhou et al 2020, Diao et al 2020), twenty-one patients with severe or critical COVID-19 pneumonia were treated recently with tocilizumab IV (400 mg) plus SOC that consisted of lopinavir, methylprednisolone, other symptom relievers, and oxygen therapy as recommended by the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Sixth Edition) (Xu X et al 2020). No deaths were reported, and after tocilizumab treatment, 75% of patients exhibited lowered O_2 intake, 90% of patients showed significant improvement in lung opacities and 85% of patients showed significant decrease in C-reactive protein (CRP) levels (Xu X et al 2020). Recently, it has been shown that monocyte-derived IL-1β and IL-6 (downstream of IL-1β) differentially regulate CRS and neurotoxicity associated with CAR-T therapy, with the IL-1 receptor antagonist anakinra abolishing both CRS and neurotoxicity, resulting in substantially extended leukemia-free survival (Giavridis et al 2018, Norelli et al 2018). The IL-6R blockade with tocilizumab in alleviating COVID-19 symptoms together with the role of IL-1β, upstream of IL-6, in the pathophysiology of CAR-T-induced CRS strongly suggests that IL-b blockade might alleviate the cytokine storm following COVID-19 that promotes pneumonia, ARDS and worse outcome.

Canakinumab is a high-affinity human monoclonal anti-human IL-1β antibody of the IgG1/k isotype which is marketed and under ongoing development for the treatment of IL-1β driven inflammatory and oncologic diseases. By binding specifically to human IL-1β, canakinumab blocks the interaction of IL-1β with the IL-1 receptor (IL-1R), leading to inhibition of its downstream targets, thereby preventing IL-1β-induced gene activation and the production of downstream inflammatory mediators such as IL-6 and CRP. Canakinumab, first registered for the treatment of cryopyrin-associated auto inflammatory syndrome (CAPS) in the United States on 17 Jun 2009, ameliorates IL-1β -mediated inflammation and was shown recently in the Phase 3 CANTOS trial to significantly reduce major adverse cardiovascular events and lung cancer incidence and mortality (Ridker et al 2017).

Taken together, evidence including: (1) the central role of IL-1β and IL-1β-driven inflammation in the pathophysiology of ARDS; (2) the increased morbidity and mortality of COVID-19 patients with chronic underlying inflammatory conditions (cardiovascular disease, diabetes) who develop pneumonia; (3) the CANTOS-trial data in cardiovascular disease and lung cancer; and (4) the excellent safety profile of canakinumab, supports the urgent need to evaluate canakinumab in COVID-19 patients with pneumonia and cytokine release syndrome in the setting of SARS-CoV-2 infection.

Based on recent observations in severe and non-severe COVID-19 patients and historical data (Meduri et al 1995, Park et al 2001, Beigel et al 2005, Bouros et al 2005, Tumpey et al 2005, He et al 2007, Kobasa et al 2007, Perrone et al 2008, Lau et al 2013, Min et al 2016, Alosaimi et al 2020, Thevarajan et al 2020) with other infectious pathogens that cause respiratory distress,

[redacted]

[redacted]

storm in the lungs of severely infected patients resulting in inflammation-driven ARDS and associated pneumonia. [redacted] will result in the following:

- Decreased severe events (intubation or death) in patients who develop COVID-19 pneumonia
- Decreased pulmonary vascular permeability occurring as a result of lung injury
- [redacted]
- Potential impact on cardiac damage as a result of inflammation
- [redacted]

This study is designed to assess whether canakinumab can safely and effectively be used to mitigate, treat, or cure COVID-19-induced pneumonia or limit the harm of the COVID-19 pandemic in accordance with the Secretary of the Department of Health and Human Services' (HHS's) Declaration under the Public Readiness and Emergency Preparedness Act (PREP Act) for medical countermeasures against COVID-19 (COVID-19 Declaration) effective February 4, 2020. The purpose of this study is to test whether canakinumab results in clinical benefit in hospitalized patients who develop COVID-19-induced pneumonia.

If this protocol is approved by the Food and Drug Administration (FDA), this study will be authorized to proceed under an approved investigational new drug application (IND) in accordance with the public health and medical response of FDA, an Authority Having Jurisdiction as described under the PREP Act, to prescribe, administer, deliver, distribute or dispense this covered countermeasure as defined by and following the HHS's COVID-19 Declaration.

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of canakinumab in the treatment of hospitalized patients with COVID-19-induced pneumonia and CRS. The study will also evaluate the morbidity and mortality in patients with COVID-19 pneumonia due to the inflammatory response to SARS-CoV-2.

[redacted]

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective To demonstrate the benefit of canakinumab + standard of care (SOC) in increasing chance of survival without ever requiring invasive mechanical ventilation among patients with COVID-19-induced pneumonia and CRS	**Endpoint for primary objective:** Clinical response, defined as survival without ever requiring invasive mechanical ventilation from Day 3 (inclusive) up to Day 29 (inclusive).
Secondary Objective(s) To demonstrate the benefit of canakinumab in reducing 4-week case fatality rate (CFR) among patients with COVID-19-induced pneumonia and CRS regardless of other subsequent clinical interventions	**Endpoint(s) for secondary objective(s):** COVID-19-related death during the 4-week period after study treatment
To evaluate change in clinical serologic measurements related to CRS in COVID-19 patients with pneumonia	• Adjusted geometric mean ratio to baseline overtime up to Day 29 in the following clinical chemistry measurements: • CRP • Serum ferritin • D-dimer
To evaluate safety of canakinumab in patients with COVID-19-induced pneumonia and CRS	Number of participants with Adverse Event (AE), serious adverse events (SAE), clinically significant changes in laboratory measures, and vital signs
[redacted]	

Objective(s)	Endpoint(s)
[redacted]	

2.1 Primary estimands

The primary clinical question of interest is: Does canakinumab + SOC increase the chance of survival without ever requiring invasive mechanical ventilation among patients with COVID-19-induced pneumonia and CRS after start of treatment, regardless of other subsequent clinical interventions?

The justification for this primary estimand is that it captures the clinical outcome of most interest after canakinumab administration, which reflects also any effects of additional subsequent interventions potentially due to such clinical decision. In the ongoing COVID-19 pandemic with evolving treatment guidelines and healthcare system burdens, this primary estimand is deemed better to reflect actual clinical practices. In addition, the IV delivery of canakinumab is expected to result in a fast decrease in pharmacologically active IL-1β and to reduce L-1β signaling to marginal levels within hours. However, clinical signs or symptoms within the 24 hours after treatment may not necessarily reflect such pharmacological effect yet. Therefore, only clinical status starting from Day 3 will be considered for the primary endpoint.

The primary estimand includes the following components:

Population: Patients with COVID-19-induced pneumonia and CRS.

Endpoint: Clinical response, defined as survival without ever requiring invasive mechanical ventilation from Day 3(inclusive) up to day 29(inclusive). A patient will be defined as a non-responder if the worst clinical status at any time from Day3 (inclusive) up to Day 29 (inclusive) is requiring invasive mechanical ventilation or death (category 6, 7 or 8 on the WHO 9-point ordinary scale of clinical status).

[redacted]

Treatment of interest: The randomized study treatment (canakinumab or placebo) added onto SOC with or without additional subsequent clinical interventions.

Handling of intercurrent events:

The treatment policy strategy will be adopted for primary analysis.

- Clinical interventions (e.g. mechanical ventilator, oxygen, intubation) newly administered as escalated SOCs corresponding to the progression of disease are integrated in efficacy evaluation based on the 9-category ordinal scale of clinical status.
- Other new or change in strength of concomitant interventions will not be adjusted for primary analysis.
- Early discontinuation from study or lost to follow up before Day 29: A patient will be considered as responder if did not require invasive mechanical ventilation any time on or after Day 3 and meets at least one of the following two criteria:
  1. The patient was discharged from hospital with clinical status of 0 or 1
  2. The last clinical status was on Day 15 or later and better than baseline

  Patient will otherwise be considered as non-responder.

Summary measure: Difference and Odds-ratio comparing response rates in the canakinumab and placebo groups.

2.2 Secondary estimands

The key secondary clinical question of interest in this study is: Does the administration of canakinumab reduce 4-week mortality among patients with COVID-19-induced pneumonia and CRS, regardless of other subsequent clinical interventions?

The justification for this secondary estimand is that mortality currently represents the main epidemiological and clinical concern for COVID-19 patients and accumulating evidences suggest coexistence of CRS with severe COVID-19-induced pneumonia. Subsequent clinical interventions, including intensive cares when a patient become terminally ill, reflect actual clinical practices, whose needs, scope and effectiveness could potentially be related to the earlier decision of canakinumab administration.

The key secondary estimand includes the following components:

Population: Patients with COVID-19-induced pneumonia and CRS.

Endpoint: COVID-19-related death during the 4-week period after study treatment

Treatment of interest: The randomized study treatment (canakinumab or placebo) added onto SOC with or without additional subsequent clinical interventions.

Handling of remaining intercurrent events:

The treatment policy strategy will be adopted for this key secondary analysis.

- Effect of other subsequent clinical interventions will not be adjusted
- Early study discontinuation or lost to follow-up before Day 29: A patient will be considered as survivor if discharged from hospital with clinical status of 0 or 1

Otherwise, the patient will not be included in this key secondary analysis.

[redacted]

Summary measure: Difference and Odds-ratio comparing 4-week CFR in the canakinumab and control groups.

3 Study design

This is a multicenter, double-blind, randomized, placebo-controlled study to assess the efficacy and safety of canakinumab plus SOC compared with placebo plus SOC in adult patients (for US only: patients ≥ 12 years old) with COVID-19-induced pneumonia and CRS (Figure 3-1).

The study aims to randomize approximately 450 patients worldwide. Enrollment will stop as soon as the target number of randomized patients is reached. Based on the evolving landscape in the treatment of COVID-19, additional arms may be added to this protocol in the future.

Patients who meet the inclusion/exclusion criteria will be randomized in a 1:1 ratio to either canakinumab + SOC or placebo + SOC and can be dosed immediately after ensuring that the patient has met all eligibility criteria. Patients in the canakinumab arm will be dosed on Day 1 with canakinumab 450 mg for body weight of 40-<60 kg, 600 mg for 60-80 kg or 750 mg for >80 kg) in 250 mL of 5% dextrose infused IV over 2 hours. Patients in the placebo arm will be treated with 250 mL of 5% dextrose infused IV over 2 hours.

An informed consent (for US patients 12 - <18 years old; parent/guardian consent must be obtained and assent if applicable) will be obtained from patients before assessments solely required for the study are performed. Thereafter, eligibility criteria will be reviewed by study personnel. All patients with signed informed consent must be registered in the Interactive Response Technology (IRT) system.

[redacted] Then additional safety assessments will be performed approximately every other day during hospitalization as described in Table 8-1. Additional follow-up visits will occur on Days 15, 29, 57 and 127 either by phone, if previously discharged, or in the hospital, if still hospitalized. If a patient is hospitalized for longer than Day 29, all invasive protocol assessments will be discontinued except at Days 57 and 127, if still hospitalized. If the patient has been discharged, the patient should be phoned for follow-up and data collected as in Table 8-1. In addition, unscheduled visits are permitted after discharge, as needed.

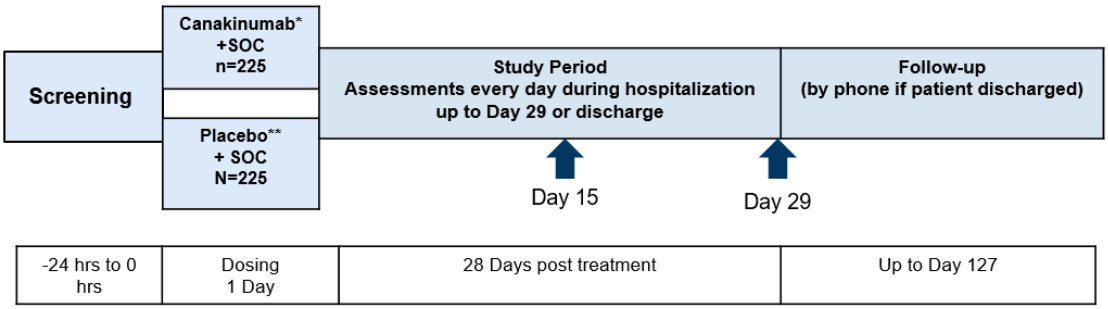
If patient discontinues the study prior to Day 29, then Day 29 assessments should be conducted on the day of discontinuation. If patient discontinues the study after Day 29, then Day 127 assessments should be conducted on the day of discontinuation.

Analyses for safety will be conducted at regular intervals using an internal Novartis data monitoring committee (DMC). Deaths and SAEs will be monitored in real time with routine pharmacovigilance and by the internal, independent DMC in order to detect any unexpected safety signal. The DMC will function independently of all other individuals associated with the conduct of this clinical trial.

Patients who do not meet the criteria for participation in this study (screen failures) will not be re-screened.

[redacted]

Figure 3-1 Study design



Study Treatment:
*Canakinumab 450 mg for body weight 40-<60 kg, 600 mg for 60-80 kg or 750 mg for >80 kg) in 250 mL of 5% dextrose infused IV over 2 hours
** 250 mL of 5% dextrose infused IV over 2 hours

4 Rationale

4.1 Rationale for study design

This randomized, double-blind, placebo-controlled design supports the rigorous assessment of efficacy as well as safety of canakinumab + SOC therapy for patients with COVID-19-induced pneumonia and CRS.

Screening Period

The screening period allows for assessment of patient entry criteria to ensure suitable patients are entered into the study, while allowing flexibility to dose the same day after ensuring eligibility criteria are met.

Study Period

On Day 1, canakinumab (450 mg for body weight of 40-<60 kg, 600 mg for 60-80 kg or 750 mg for >80 kg) versus placebo in 250 mL of 5% dextrose administered intravenously. The blinding will be performed by an unblinded pharmacist or designated person.

Due to the extended half-life of canakinumab, patients will be followed until Day 127. The endpoints included in this study measure clinical status, clinical and in-hospital outcomes, and laboratory values during the Study Period.

4.2 Rationale for dose/regimen and duration of treatment

The IV delivery of a single high dose of canakinumab, which is supported by available safety data, ensures a fast decrease in pharmacologically active IL-1β levels and is expected to reduce IL-1β signaling to low levels within hours. Adaptation of the dose to body weight using 3 weight ranges/dose levels (450, 600 and 750 mg) minimizes complexity in the dosing procedure while taking the patient's weight into consideration. The dose levels were selected based on the following considerations and will be added to standard-of-care therapy:

- In COVID-19-induced pneumonia patients, there seems to be a stage at which CRS may become a predominant factor in outcomes. The amount of released cytokines may be estimated to be about 30-60 fold above baseline values requiring a high dose. Many cytokines have been assayed and showed increased concentrations.
- Registered canakinumab doses in currently marketed indications vary from 2 to 8 mg/kg in children and from 150 to 600 mg by subcutaneous (s.c.) route in adults. The doses of 10 mg/kg or 600 mg iv canakinumab have been previously investigated in 288 patients or healthy volunteers (including children >3 years of age) as single or repeated doses in autoinflammatory conditions, gouty arthritis, asthma, type 2 diabetes mellitus, and ocular conditions in the development program. Canakinumab was safe and well tolerated in all studies, with no safety concern identified by analysis of AE, laboratory or vital signs.
- The 450 mg for body weight of 40-<60kg, 600 mg for 60-80 kg and 750 mg for >80kg dosing regimen was selected in order to reach the maximal and safe highest exposure to canakinumab of approximately 10 mg/kg. The intravenous (IV) route will give higher exposure as compared to s.c. shortly after dosing which is considered critical for treatment of CRS especially given the rapid decrease in clinical outcomes observed in some patients with COVID-19 pneumonia.
- A relatively high dose is proposed:
  - To take into account the possibility of lower drug concentrations in CRS patients (as is seen with tocilizumab, Le et al 2018)
  - To take into account the unknown diffusion in inflamed lung tissues

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

Currently, no approved treatment for COVID-19 induced pneumonia and CRS is available. A placebo-controlled study should mitigate the potential biases associated with the clinical setting and the endpoints related to the study objectives and allow for an objective assessment of canakinumab value in this indication.

4.4 Purpose and timing of interim analyses/design adaptations

Not Applicable.

4.5 Risks and benefits

Potential patient benefits

As of March 28, 2020, COVID-19 has been confirmed in 629,355 people worldwide with 28,963 deaths reported (Worldometers 2020). As of March 12, 2020, the mortality rate was calculated at approximately 3.7%, compared with a mortality rate of less than 1% from influenza. Currently, there are no approved treatments nor vaccines, and so there is an urgent need for effective treatment (Mehta et al 2020).

SARS-CoV-2 is characterized by a spherical morphology with 36 spike projections on the surface and is similar to the β-coronaviruses generally seen in bats (Ahn et al 2019). The novel coronavirus, SARS-CoV-2 uses the same receptor, ACE2 as that for SARS-CoV (cause of

[redacted]

previous corona virus epidemic), and mainly spreads through the respiratory tract. The clinical symptoms of COVID-19 patients include fever, cough, fatigue, loss of smell, and shortness of breath within 2-14 days after exposure (CDC 2020). The current SARS-CoV-2 pandemic is resulting in 10-20% of infected patients developing severe illness. The severe clinical course includes interstitial pneumonia that can abruptly evolve within a few days to ARDS and multi-organ failure. Severe infection is also associated with high elevation of acute-phase reactants, including CRP. This clinical picture of increased cytokines and multi-organ failure is consistent with CRS. Canakinumab is an IL-1β inhibitor which could improve the outcomes of patients with COVID-19-induced pneumonia and CRS based on its effect on the inflammasome pathway.

Hyper-activated innate immune responses drive tissue injury during viral infections, and increased IL-1β production via the NLRP3 inflammasome has been shown to accelerate lung pathology and fibrosis in the context of sterile inflammation or viral infection. Coronaviruses can specifically activate the NLRP3 inflammasome, and by promoting bronchial epithelial cell death, can further exacerbate inflammasome-driven IL-1β production. Bats, which act as an asymptomatic reservoir for coronaviruses, have reduced NLRP3 inflammasome activity, linking IL-1β to the organ-specific manifestations seen in humans. Increased levels of IL-1β and/or its downstream effector IL-6 have been detected in SARS-CoV and in COVID-19 patients and correlate with severity of clinical symptoms. Neutralization of IL-1β and/or its downstream cytokine IL-6 has shown benefit in preclinical models of CRS and in the clinic with patients undergoing CAR-T therapy. Furthermore, case studies using the IL-6R neutralizing antibody tocilizumab have shown benefit in treating COVID-19 patients. Neutralization of IL-1β upstream of IL-6 could address some of the additional pleiotropic tissue-destructive effects of IL-1β in the lung, and canakinumab and other IL-1 antagonists have a lower risk of infection than IL-6-targeting agents such as tocilizumab.

Accumulating evidence suggests that patients develop CRS with severe acute pneumonia due to COVID-19. Currently, there is no clinical experience with canakinumab in the treatment of SARS-CoV-2 pneumonia nor cytokine release syndrome *per se*. However, the cytokine profiling of patients with severe COVID-19 which is associated with elevated levels of IL-1, IL-2, IL-7, IL-6, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α and tumor necrosis factor-α suggests that canakinumab could improve patient outcomes (Mehta et al 2020, Zhou et al 2020).

Based on these findings, canakinumab may have a role in reducing the inflammatory response in patients with COVID-19-induced pneumonia and CRS.

Potential risks due to study medication

The risk to patients in this trial will be minimized by adherence to the eligibility criteria and close clinical monitoring, including by an internal DMC. Over 2,600 patients including approximately 480 children (aged 2 to 17 years) have been treated with canakinumab in interventional studies in Periodic fever syndromes, Still's disease, gouty arthritis, or other IL-1 beta mediated diseases, and healthy volunteers. The most frequently reported adverse drug reactions were infections, predominantly of the upper respiratory tract. The majority of the events were mild to moderate although serious infections were observed. No impact on the type

[redacted]

or frequency of adverse drug reactions was seen with longer-term treatment. Hypersensitivity reactions and opportunistic infections have been reported in patients treated with canakinumab. Neutropenia and leukopenia has also been observed with IL-1 inhibitors including canakinumab, with transient decreases to $<1x10^9$ /L observed during clinical trials with canakinumab.

In addition to experience in approved indications, over 10,000 patients were enrolled in the CANTOS study evaluating canakinumab for the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated CRP, with a cumulative exposure of 32662.6 patient-years (21745.1 patient-years for total canakinumab and 10917.5 patient-years total for placebo).

No clinically meaningful differences between canakinumab and placebo were observed for most safety topics of interest, apart from an increase in serious infections and of fatal infections/sepsis; however, the overall incidence was low. The pattern of infections was stable over time, with very few confirmed opportunistic infections distributed evenly across the treatment groups. There was no evidence of tuberculosis reactivation in canakinumab-treated patients.

The overall incidences of investigator-reported infection AEs and discontinuations due to infection AEs were comparable across the treatment groups. For investigator-reported infection SAEs, there were numerical differences of 1-2% in the overall incidence for the canakinumab 300 mg and 150 mg groups compared with placebo. Similarly, a slightly higher percentage of patients discontinued due to an infection SAE in the canakinumab 300 mg and 150 mg groups than in the placebo group. The majority of infection AEs consisted of non-serious upper respiratory tract infections which showed no clinically meaningful differences across the treatment groups. Increases in the order of 1% with canakinumab relative to placebo in the overall population were seen for certain infection events, i.e., sepsis, cellulitis, infectious pneumonias. The increase in cellulitis was seen predominately in patients with type-2 diabetes mellitus, and that of infectious pneumonias in patients with a history of asthma/chronic obstructive pulmonary disease. There was no meaningful difference between canakinumab 150 mg and 300 mg in the risk of cellulitis or infectious pneumonias; however, a higher risk of sepsis AEs with canakinumab 300 mg was observed.

Laboratory data showed an increase with canakinumab 300 mg only in mild neutrophil and platelet count abnormalities (Grade 1), with no imbalances in larger declines (Grades 2-4) in neutrophil and platelet counts, or in triglyceride levels, between 300 mg and 150 mg.

All-cause mortality was numerically lower across the three canakinumab treatment groups compared to placebo, with both fewer cardiovascular deaths and non-cardiovascular deaths. There was an increased incidence of deaths due to infection/sepsis for canakinumab 150 mg vs. placebo, although the numbers of related deaths were low overall.

The main adverse drug reaction was infection, of which the most common included viral upper respiratory tract infection, influenza, and pneumonia.

Overall, the safety and tolerability profile of canakinumab in post myocardial infarction patients was consistent with the known safety profile in the approved indications.

Known risks of canakinumab pertinent to short term use include the risks of infection (including opportunistic infection), interaction with live vaccines and the use in combination with other

[redacted]

immunosuppressant's (including TNF inhibitors) due to increased risk of serious infections. Taking into account the individual risks as outlined above, the expected risk profile of canakinumab from its mechanism of action is expected to be similar to that previously observed. Based on overall risk-benefit assessment, the very high unmet medical need and the implemented controlled setting, the current trial with canakinumab is justified.

There is a limited amount of data from literature and post-marketing reports on the use of canakinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. The risk for the fetus/mother is unknown. Monoclonal antibodies such as canakinumab actively cross the placenta and are detectable in the fetus, predominantly in the second and third trimesters of pregnancy. Based on limited human data, canakinumab levels were detected in cord and neonatal blood. The clinical impact of this is unknown. However, administration of live vaccines to newborn infants exposed to canakinumab *in utero* is not recommended for 16 weeks following the mother's last dose of canakinumab before childbirth.

It is not known whether canakinumab is transferred into breast milk. There are no data on the effects of canakinumab on the breastfed child or the effects of canakinumab on milk production. Animal studies have shown that a murine anti-murine IL-1 beta antibody had no undesirable effects on development in nursing mouse pups.

For a comprehensive assessment of the risks of canakinumab, refer to the Investigator's Brochure (IB).

Study specific risks

Protocol-mandated invasive procedures performed during this study include blood sampling for the collection of safety laboratory parameters, [redacted].

Chest radiograph or CT scan are required for the diagnosis of COVID-19-induced pneumonia prior to study entry and during follow-up. Radiation exposure occurs during each procedure. The radiation received during one x-ray is the same as 1 to 2 weeks of normal radiation received in everyday life. The radiation received during one CT exam is the same as 2 - 10 years of normal radiation received in everyday life, depending on the body parts included. Some people may experience claustrophobia while inside the CT machine.

Oversight committees

An internal DMC will be established comprising of an independent (of the study) group of individuals from Novartis who have experience and expertise in the management of patients within this disease area, experience in statistical methods, safety monitoring and in the monitoring of randomized clinical trials who will review safety data provided by the study team at regular intervals, to ensure the safety of patients enrolled in this new disease area.

[redacted]

5 Study Population

The study population includes adult (for US only: patients ≥ 12 years old) male and female patients who are hospitalized and diagnosed with COVID-19-induced pneumonia and CRS.

5.1 Inclusion criteria

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

1. Male or female
2. Adults ≥ 18 years old (for US only: patients ≥ 12 years old)
3. Body weight ≥ 40 kg
4. Informed consent must be obtained prior to participation in this study. For US patients 12 - <18 years old; parent/guardian consent must be obtained and assent if applicable.
5. Clinically diagnosed with the SARS-CoV-2 virus by PCR or by other approved diagnostic methodology within 7 days prior to randomization.
6. Hospitalized with COVID-19-induced pneumonia evidenced by chest x-ray or CT scan (taken within 5 days prior to randomization) with pulmonary infiltrate.
7. $SpO_2 \leq 93\%$ on room air, or arterial oxygen partial pressure (PaO_2)/fraction of inspired oxygen (FiO_2) < 300mmHg (1mmHg=0.133kPa) (corrective formulation should be used for higher altitude regions (over 1000m)).
8. C-reactive protein ≥20 mg/L or ferritin level ≥600 μg/L.

5.2 Exclusion criteria

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

1. History of hypersensitivity to canakinumab or to biologic drugs.
2. Intubated and on mechanical ventilation (invasive) at time of randomization
3. Treatment with immunomodulators or immunosuppressant drugs, including but not limited to tocilizumab, TNF inhibitors and anti-IL-17 agents within 5 half-lives or 30 days (whichever is longer) prior to randomization with the exception of anakinra which is excluded within 5 half-lives only. *Note: Immunomodulators (topical or inhaled) for asthma and atopic dermatitis and corticosteroids (any route of administration) are permitted*
4. Suspected or known untreated active bacterial, fungal, viral, or parasitic infection with the exception of COVID-19
5. Neutropenia with ANC <1000/mm^3
6. 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
7. In the opinion of the investigator, progression to death is imminent and highly likely within the next 24 hours, irrespective of the provision of treatments
8. Current participation in any other investigational trials

[redacted]

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

The study will enroll patients who require hospitalization and will receive, in addition to the local SOC, canakinumab or placebo. The total duration of treatment will be approximately 2 hours (Table 6-1).

Investigational treatment:

Canakinumab dose as per Table 6-1 in 250 mL of 5% dextrose infused IV over 2 hours.

Placebo:

250 mL of 5% dextrose infused IV over 2 hours

Table 6-1 Canakinumab dose by body weight

Patient's weight (kg)	Dose of canakinumab	Volume of 150 mg/mL
> 80	750 mg	5.0 mL
60 to 80	600 mg	4.0 mL
40 to < 60	450 mg	3.0 mL

Canakinumab or placebo will be prepared by the unblinded pharmacist. Details on the requirements for storage and management of study treatment, and instructions to be followed for participant numbering, prescribing/dispensing, and taking study treatment are outlined in the Pharmacy Manual.

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Supply of study treatment

Investigational and control drugs will be provided as described in Table 6-2.

Table 6-2 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
ACZ885 150mg/1ml	Concentrate for solution for infusion	Intravenous use	Open label bulk supply; vials	Sponsor (global)

Dextrose 5% will be used at the site to dilute investigational drug or as placebo.

[redacted]

6.1.4 Treatment arms/group

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

- **Investigational treatment:** Canakinumab dose as per Table 6-1 in 250 mL of 5% dextrose infused IV over 2 hours.
- **Reference treatment:** 250 mL of 5% dextrose infused IV over 2 hours.

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.

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.

The patient must be told to notify the Treating Physician about any new medications that he/she takes after the start of canakinumab.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Patients in this study will be enrolled to canakinumab or placebo, in addition to SOC per local practice, which may include anti-viral treatment, corticosteroids and supportive care.

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

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

6.2.2 Prohibited medication

The following medications are prohibited:

- Up to Day 29, concomitant use of biologics including anakinra, tocilizumab, 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.

For additional information, please refer to the IB.

[redacted]

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. 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 (ICF) form, the participant is assigned to the next sequential Participant No. available.

6.3.2 Treatment assignment, randomization

At Randomization visit, all eligible patients will be randomized via IRT to one of the treatment arms. A designated site staff member (preferably the pharmacist conducting the blinding) other than the investigator or study staff involved in safety and efficacy assessments or eCRF completion will contact the IRT after confirming that the patient 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, or by a delegate under Novartis supervision, 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.

If a patient discontinues before Randomization, the IRT should be notified within two days and the reason for not being randomized should be recorded on the appropriate Case Report Forms.

Randomization will be stratified by country to ensure a balanced allocation of patients to treatment groups within the strata.

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

6.4 Treatment blinding

This is a double-blind randomized treatment trial. Participants, all site staff (including study investigator and study nurse), persons performing the assessments, and clinical trial team will remain blind to the identity of the treatment from the time of randomization until database lock for primary analysis.

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 will receive the treatment arm assigned by the IRT system during the randomization transaction.

[redacted]

Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

The following unblinded sponsor roles are required for this study:

- DMC members
- Bioanalyst
- Independent statistician
- Independent programmer

The independent DMC committee and the independent analysis team (independent statistician, independent programmer) will be allowed to access treatment information via a request to the randomization office for the purpose of creating, reviewing and assessing unblinded interim results. More details will be provided in a DMC charter.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure until clinical database lock.

Following final database lock all roles may be considered unblinded. See the blinding/unblinding table for an overview of the blinding/unblinding plan.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted. Please refer to Section 6.1 for treatment guidance.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

[redacted]

6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of AEs in this patient population.

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

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. 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

[redacted]

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/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- 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 in packaging as described under investigational and control drugs section.

Study drug will be packed and labeled as ACZ885 and supplied as open label bulk supplies. Each box will contain multiple vials of ACZ885 150mg/1ml. The box can be used for treatment of multiple patients. However, each vial intended for one patient should not be used for another patient.

Preparation of the investigational drug must be done in a separate space/room where study personnel have no access during time of preparation.

6.7.1 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 designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified in the IB.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis 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 pharmacist or other qualified site personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log which will be kept in a Pharmacy File in a secured location to which no blinded site staff would have access to.

Study treatment will be prepared by an independent pharmacist or qualified site personnel in order to ensure treatment blinding as described in Section 6.1.

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

[redacted]

accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.2 Instruction for prescribing and taking study treatment

Please refer to Section 6.1 for treatment guidance.

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 capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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 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 (IN) 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 (For US patients 12 - <18 years old; parental consent and adolescent assent)
- As applicable, Pregnancy Outcomes Reporting Consent for female subjects

[redacted]

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. [redacted] It is required as part of this protocol that the Investigator presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

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

[redacted]

8 Visit schedule and assessments

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

Participants should be seen or phoned 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. At the day of discharge from the hospital, all assessments should be conducted per Table 8-1. In addition, contact information for the patient and/or legal representatives should be obtained for the follow-up visits.

Screening assessments are to be taken as indicated in Table 8-1 prior to randomization and are considered baseline measurements. Patients who meet the inclusion/exclusion criteria may be dosed immediately after obtaining the baseline measurements.

[redacted]

Table 8-1 Assessment and Procedures Schedule (Baseline to 18-week safety follow up)[13]

Visit Day	-1 (0-24 hrs prior to randomization)[1]	1	2	Every day during hospitalization until Day 29 or discharge (whichever is earlier)	15[2]	29 or Day of Discharge[2]	Day 57[2] (±7 days)	127[2] (±7 days)/ End of Study
Informed consent (including optional genetic ICF and assent if applicable)[3]	x							
Inclusion/Exclusion criteria	x	x[4]						
Demographics / medical history	x							
SARS-CoV-2 virus testing (local labs)	x[8]	Record all testing, if obtained						
SARS-CoV-2 nasopharyngeal samples (central lab)	x					x		
Vital signs: Heart rate, Respiratory rate, Oxygen saturation or PaO_2/FiO_2, Systolic/diastolic blood pressure, Body temperature[5]	x	x[4]	x	x	x	x		
Height, weight	x							
Physical exam[6]		s[4]	s		s	s	s	
Clinical status evaluation with 9-point ordinal scale (e.g. oxygen requirement, invasive/non-invasive mechanical ventilation, additional organ support)		x[4]	x	x	x	x	x	x
Hematology (local labs)	x		x	x (every other day e.g., Days 3, 5, 7, etc.)	x	x	x	
Clinical chemistry, CRP, ferritin, d-dimer (local labs)	x		x	x (every other day e.g., Days 3, 5, 7, etc.)	x	x	x	
Pregnancy test[7] (local labs)	s					s	s	s
Chest x-ray or CT scan[8]	x	Record all pulmonary imaging if obtained						
ECG (local)	s		s			s		
Adverse events	x	x[4]	x	x	x	x	x	x
Prior/concomitant medications/non-drug therapy (i.e. oxygen)	x	x[4]	x	x	x	x	x	x

[redacted]

Visit Day	-1 (0-24 hrs prior to randomization)[1]	1	2	Every day during hospitalization until Day 29 or discharge (whichever is earlier)	15[2]	29 or Day of Discharge[2]	Day 57[2] (±7 days)	127[2] (±7 days)/ End of Study
Randomization		x						
Study drug administration		x[9]						
Days from onset of symptoms to study treatment		x[4]						
[redacted]								

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. After informed consent is obtained (or assent if applicable), baseline measurements should be collected between 0 to 24 hours prior to canakinumab/placebo dose, unless otherwise specified.

2. If patient is discharged prior to Day 29, then all assessments listed for Day 29 should be conducted on the Day of Discharge. Visits at Days 15, 29, 57 and 127 should be conducted via phone for patients who were discharged prior to the visit (+/- 3 days). These phone visits should only collect Clinical status evaluation with 9-point ordinal scale, Adverse events, Concomitant medications, [redacted] whereas vital signs, physical exam, laboratory tests (including pregnancy test), [redacted] will not be conducted. If the patient remains hospitalized, however, all assessments noted in the table should be conducted on the visit day noted.

[redacted]

Visit Day	-1 (0-24 hrs prior to randomization)[1]	1	2	Every day during hospitalization until Day 29 or discharge (whichever is earlier)	15[2]	29 or Day of Discharge[2]	Day 57[2] (±7 days)	127[2] (±7 days)/ End of Study
3. Informed consent must be signed (within 0-48 hours prior to randomization) and prior to any study-related procedures, unless otherwise noted or previously conducted during hospitalization. 4. All baseline (Visit Day 1) assessments must have been conducted prior to dosing with canakinumab (except Days from onset of symptoms to study treatment and [redacted] 5. Vitals signs should be recorded at a consistent time once each day for a patient (i.e. morning, afternoon or evening) and upon significant clinical changes. Respiratory rate and oxygen saturation only if not on mechanical ventilation, or PaO_2/FiO_2. After Day 1, if patient is receiving supplemental oxygen (not on invasive ventilation), then oxygen flow rate and/or FiO_2 and oxygen saturation to be collected. 6. A complete physical examination will be performed for baseline, for remaining time points; targeted physical examination, per investigator discretion, and may be performed. 7. Pregnancy test: only for females of childbearing potential, serum pregnancy test (serum hCG) will be performed at baseline visit. Urine or serum pregnancy test to be performed at other visits, if hospitalized. 8. Results confirming positive SARS-CoV-2 virus by PCR or by other approved diagnostic methodology available within 7 days and chest x-ray or CT scan within 5 days prior to randomization may be used for eligibility. 9. Canakinumab may be dosed immediately after obtaining all baseline measurements and confirming eligibility. [redacted] 13. Unscheduled visits are permitted after discharge, as needed.								

[redacted]

8.1 Screening

No rescreening will be permitted.

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 SAE section 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 CRF.

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 Health Authorities.

8.2.1 Demographic/baseline characteristics 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, and updated at the baseline visit. Any changes to the ongoing medications or any new concomitant medications will be recorded in CRF on an ongoing basis throughout study participation.

[redacted]

8.3 Efficacy

8.3.1 Clinical status (9-point ordinal scale)

Assessment of clinical status using a 9-point ordinal scale (WHO 2020b) will be recorded at baseline on Day 1 before the start of the study treatment and then again once per day through Day 29 of the Study Period, if hospitalized (Appendix 1). 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 the previous day's data, and the worst score is recorded as the score for Day 2). In addition, on Day 29 or the Day of discharge, clinical status on Day 29 or the Day of discharge should be recorded.

Table 8-2 Clinical status (9-point ordinal scale)

Patient State	Descriptor	Score
Uninfected	No Clinical or virological evidence of infection	0
Ambulatory (not in hospital or in hospital and ready for discharge)	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy (defined as $SpO_2 \geq 94\%$ on room air)	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 (renal replacement therapy), ECMO (extracorporeal membrane oxygenation)	7
Dead	Death	8

8.3.2 Vital signs and oxygen saturation and use

Vital sign measurements include respiratory rate, pulse rate, systolic and diastolic blood pressure, and body temperature. Vitals signs should be recorded at a consistent time once each day for a patient (i.e. morning, afternoon or evening) and upon significant clinical changes.

[redacted]

Peripheral oxygen saturation on room air should also be measured at the same time as the vitals, if not on supplemental oxygen. After Day 1, 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.

[redacted]

8.3.5 Appropriateness of efficacy assessments

Efficacy endpoints are those employed in other studies of patients with COVID-19 pneumonia (WHO 2020b).

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 (Section 10.1).

[redacted]

8.4.1 Laboratory evaluations

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

8.4.1.1 SARS-CoV-2 virus testing

For the Screening inclusion criterion, SARS-CoV-2 virus should be measured by PCR or by other approved diagnostic methodology ≤ 7 days prior to randomization by local lab. Documentation of the method used should be available in the source notes.

If additional testing is conducted locally, results should be recorded in the CRF.

8.4.1.2 Laboratory evaluations

Laboratory evaluations will be performed by the local lab.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured according to the assessment schedule in Table 8-1.

Chemistry

BUN/urea, creatinine, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transpeptidase, lactate dehydrogenase, sodium, potassium, chloride, calcium, bicarbonate, phosphorus, total protein, albumin, glucose, uric acid will be measured according to the assessment schedule in Table 8-1. If a given test is not available locally, this should be documented on the eCRF.

Additional markers of inflammation: CRP, ferritin, and d-dimer should be collected in accordance with Table 8-1.

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator (in consultation with the sponsor) and shall be based, in part, upon the nature and degree of the observed abnormality. In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.

All patients with laboratory tests containing clinically significant abnormalities should be followed until the values return to within the normal ranges or until a clinical explanation is identified, even after study medication has discontinued.

8.4.2 Physical exam

A complete physical examination will be performed for baseline measurement at the time point defined in Table 8-1. It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes,

[redacted]

extremities, vascular and neurological. Then, for remaining time points, targeted physical examination, per investigator discretion, may be performed.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to informed consent being granted must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after informed consent is given which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's eCRF.

8.4.3 Height, weight

Height in centimeters will be measured at the Screening visit as specified in the table of assessments (Table 8-1).

Body weight (to the nearest 0.1 kilogram in indoor clothing, but without shoes) will be measured at the Screening visit as specified in the table of assessments (Table 8-1).

8.4.4 Electrocardiogram (ECG)

An ECG will be taken locally as specified in the Table 8-1

The ECG should be recorded after 10 minutes of rest in the supine position to ensure a stable baseline.

Each ECG tracing should be labeled with study number, patient initials patient number, date and time, and filed in the study site source documents.

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

8.4.5 Pregnancy and assessments of fertility

All women of child-bearing potential (except if already confirmed pregnant) will have a serum pregnancy test at Screening and urine or serum pregnancy test at subsequent designated visits (Table 8-1), if hospitalized. Pregnancy tests will be conducted at the local lab and documented in the source documents.

8.4.6 Chest x-ray or CT scan

Standard chest x-ray or CT scan will be performed for eligibility except for those who have had a valid x-ray or CT scan done within 5 days prior to randomization. The results must be known prior to randomization to determine the patient's eligibility for the study. Additional chest x-rays (or CT scan) will be performed, as needed.

Chest x-ray or CT scan results 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 marketed compound where the safety profile has been established. The assessments are relevant to the critical care setting and will enable determination of therapeutic response in this setting.

[redacted]

8.5 Additional assessments

8.5.1 SARS-CoV-2 nasopharyngeal samples

Viral load may be measured by assessment of nasopharyngeal swabs sent to the central lab at time points designated in the assessment schedule (Table 8-1). Nasopharyngeal swabs should be taken in both nostrils or in the same nostril throughout the trial (whenever possible).

Laboratory Manuals will be provided with detailed information on sample collection, handling, and shipment

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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

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

Study treatment must be discontinued under the following circumstances

- Participant/guardian decision
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unblinding

- Emergence of adverse events that in the judgment of the investigator, taking into account the participant's overall status, prevent the participant from continuing participation in the study
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study
- Severe hypersensitivity reaction occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension. Immediate interruption of the infusion to administer study treatment is required in such cases.

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

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' section). **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, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. 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.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

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 (WoC) 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

[redacted]

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

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

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

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

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

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

9.1.3 Lost to follow-up

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

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

Unexpected, significant, or unacceptable safety risk to participants enrolled in the study

Decision based on recommendations from the internal data monitoring committee (DMC) after review of safety and efficacy data

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

9.2 Study completion and post-study treatment

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

[redacted]

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 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.

[redacted]

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

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

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

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

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

Adverse event monitoring should be continued to the end of study visit.

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 Investigator's Brochure (IB).

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

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

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

10.1.2 Serious adverse events

An 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:

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

[redacted]

- requires in-patient 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.

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. SAE reporting

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 within 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 within 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.

[redacted]

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, an associate from the Chief Medical Office and Patient Safety (CMO&PS) Department may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an 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, or is enrolled while pregnant, 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, if a pregnant patient is enrolled or a patient becomes pregnant after signing the informed consent, this must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to 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.

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 (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.

[redacted]

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 sections.

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 16-1 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 GGT) to confirm elevation.

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

[redacted]

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 with 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 and defined in the Assessment Schedule (Table 8-1) 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 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 eCRFs) (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.

11.2 Database management and quality control

Novartis personnel (or designated 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 World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by the Novartis IRT, who will also manage the database. The data will be sent electronically to Novartis) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer

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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 an initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, 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 in conducting these activities. Continuous monitoring of each site's data will be performed throughout the conduct of the study. 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 the respective source documents. The investigator must also keep the original informed consent form signed by the participant and/or legal representative (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 verification for the presence of all informed consents, 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

The primary analysis of the study will be performed after all patients finished day 29 assessment or discontinued early from study before Day 29. The final analysis will happen after all patients complete the study.

Safety summaries will be produced for regular DMC safety monitoring according to the schedule of DMC meetings.

[redacted]

Unless if otherwise clarified, descriptive summaries for categorical data will include frequencies and percentages, and continuous data will be presented with mean, standard deviation, median, minimum, and maximum. For selected parameters, 25th and 75th percentiles may also be presented.

Differences, relative risks (RR) and odds ratios (OR) for the comparisons between the two treatment arms will be presented with 2-sided 95% confidence interval (CI). P-values will be presented if formal hypothesis test is performed.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all participant to whom study treatment has been assigned by randomization. According to the intent to treat (ITT) principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure. Efficacy analyses will be performed on the FAS.

The Safety Set includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received. The Safety Set will be used in the analysis of all safety variables.

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 for the FAS. Detailed list of demographic and baseline characteristic parameters will be included in SAP.

12.3 Treatments

Analyses on treatment and exposure will be on safety set.

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 analysis for this study will be conducted on the FAS using treatment policy strategy.

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

The primary estimand, including primary endpoints, are defined in Section 2.1 of this protocol. The primary endpoint will be derived based on the 9-point ordinal scale of clinical status (Appendix 1).

Additional details on primary endpoint derivation will be included in SAP.

[redacted]

12.4.2 Statistical model, hypothesis, and method of analysis

[redacted]

12.4.3 Handling of remaining intercurrent events of primary estimand

Not Applicable.

12.4.4 Handling of missing values not related to intercurrent event

If a patient died first day after study treatment, the patient will be excluded from the primary analysis. Other missing data handling rules, if needed, will be specified in the SAP.

12.4.5 Sensitivity analyses for primary endpoint/estimand

[redacted]

12.4.6 Supplementary analysis

Not Applicable.

12.4.7 Supportive analyses

The primary analysis (without hypothesis test) will be repeated by age groups (≥65 years vs. <65 years) and by different baseline clinical status subpopulations.

[redacted]

12.5 Analysis of secondary endpoints/estimands

12.5.1 Key secondary endpoint

The key secondary endpoint is the COVID-19 related death during the 4-week period after study treatment. Hypothesis test for the key secondary analysis will be performed if and only if the null hypothesis for the primary analysis is rejected.

The null hypothesis for the key secondary analysis is that there is no difference in the COVID-19 related death rate (i.e. CFR) in patients treated with canakinumab compared to patients on placebo. The test of the hypothesis will be based on a logistic regression model adjusted for treatment, region and the baseline clinical status. The null hypothesis will be rejected if the observed p-value for treatment comparison (based on the CFR ratio) is less than the significance level of 0.05. Model-based estimates of the CFR and their 95% confidence intervals (CIs), estimate of the CFR ratio and 95% CI, and p-value for comparing canakinumab vs. placebo will be provided.

The number and percent of patients with COVID-19 related death during the 4-week period will also be provided by treatment arms.

The key secondary efficacy analysis is based on FAS. Patients who are lost to follow-up or discontinue early from study before Day 29 will be deemed as survivor if the latest clinical status is 0 or 1 on the 9-point ordinal scale. Otherwise, the patient will not be included in the analysis.

A sensitivity analysis will be provided by considering all patients who lost to follow-up or discontinue early from study before Day 29 as survivors.

12.5.2 Other Secondary objectives and 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 variables that of the categorical type.

12.5.3 Safety endpoints

All safety analyses will be based on the safety set including all data collected on or after the first dose date.

Adverse events

The number (and percentage) of patients with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind 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.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

[redacted]

Similar summaries will be provided for study medication related adverse events, death, serious adverse events.

The number (and proportion) of participants with adverse events of special interest/related to identified and potential risks (i.e. Infections, Opportunistic infections, Drug induced liver injury, Immunosuppressants combination therapy toxicity, Interactions with vaccines, Macrophage activation syndrome) will be summarized by treatment.

Deaths, serious AEs, and study medication related AEs will be listed separately.

Vital signs

Vital signs data will be summarized by treatment and visit.

Clinical laboratory evaluations

Laboratory data will be summarized by treatment and visit.

12.5.4 Biomarkers

Adjusted geometric mean ratio to baseline in serum ferritin, CRP and D-dimer will be reported by treatment arm and visit.

[redacted]

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[redacted]

12.6 Interim analyses

Summaries of safety data will be produced for DMC safety monitoring when needed.

12.7 Sample size calculation

12.7.1 Primary endpoint(s)

Approximately 450 patients will be randomized to canakinumab + SOC or placebo + SOC in a 1:1 ratio.

Patients infected with COVID-19 exhibit a wide range of clinical severity. With recent initial outbreak and evolving pandemic situations, limited data is available to precisely estimate the rate of disease progression after hospital admission for the population of interest under SOC. The CDC reported 31.4% hospitalizations and 11.5% ICU admissions (among patients with known hospitalization and ICU admission status) in the United States between February 12 and March 16, 2020 (CDC COVID Response Team 2020). An earlier summary (Wu and McGoogan 2020) of 72314 diagnosed cases in China estimated about 81% mild cases, 14% severe cases, 5% critical case and an overall case-fatality rate of 2.3%. A worldwide tally by WHO as of March 12th, 2020 estimated a mortality rate of 3.7% with 125,048 confirmed cases. A study by Zhou et al (2020) based on complete follow-up of 191 in-hospital patients during the early outbreak of COVID-19 in China reported an in-hospital CFR as high as 28%, while other studies reported much smaller CFR with incomplete follow-up data. Detailed summaries of disease progression time course during hospitalization or by disease status based on large samples, however, were not found.

With this study enrolling only hospitalized patients with COVID-19 induced pneumonia and CRS, and assuming that more than half of this patient population will likely require invasive mechanical ventilation, the true response rate for the control arm of this study is considered most likely in the range from 20% - 50%, while the CFR is not likely to be more than 25%.

Invasive mechanical ventilation is a radical departure from the physiology of breathing spontaneously, which put patients under risks of various immediate and long-term complications (Soni and Williams 2008) regardless of the survival outcome. The benefits of canakinumab for COVID-19 patients is considered clinically meaningful if it leads to an absolute increase of 15% patients who survived without ever requiring invasive mechanical

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ventilation. A 4-week CFR reduction by half (i.e. relative risk=0.5) is also considered meaningful clinical benefit outweighing the known risks of canakinumab.

Assuming the true response rate for the control arm lies within the range of 20% - 50%, a total sample size of 450 and 1:1 randomization ratio will provide at least 89% power to detect the minimum clinically meaningful benefit of interest.

Table 12-1 Power for primary analysis under varying assumptions (sample size = 450)

Response Rate (%)		Clinically meaningful benefits			Power (2-side α=0.05)
Control	ACZ885	difference	OR	RR	
50	65	15	1.86	1.3	89%
40	55	15	1.83	1.38	89%
30	45	15	1.91	1.5	90%
20	35	15	2.15	1.75	94%

Early discontinuation from study before patient recovery is considered unlikely in this study, hence the sample size is not adjusted for attrition. Blinded sample size reevaluation may be performed to confirm the assumptions for the sample size calculation, based on which the sample size may be updated without inflation of type I error.

12.7.2 Secondary endpoint(s)

Using a hierarchical testing procedure for familywise 2-sided type I error control at 0.05, the hypothesis test in key secondary analysis on 4-week CFR will be performed if and only if null hypothesis in primary analysis is rejected. The conditional power for detecting a 50% drop of 4-week CFR are evaluated under different assumptions on control arm 4-week CFR.

Table 12-2 Power for key secondary analysis (sample size = 450)

CFR (%)		Clinically meaningful benefits			Power (2-side α=0.05)
Control	ACZ885	difference	OR	RR	
25	12.5	-12.5	0.43	0.5	92%
20	10	-10	0.44	0.5	83%
15	7.5	-7.5	0.46	0.5	70%

Cases of lost to follow up before patient's recovery (clinical status = 0 or 1 on the 9-point ordinal scale) and before Day 29 is expected to be minimal. Sample size adjustment for key secondary analysis is not planned.

There is no formal hypothesis test or power consideration for other secondary analysis.

[redacted]

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

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the 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, EudraCT etc.).

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

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System 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.

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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.

[redacted]

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16 Appendices

16.1 Appendix 1: 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

(WHO 2020b)

[redacted]

[redacted]

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) • 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 is higher)

*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

[redacted]

Table 16-2 Follow up requirements for liver laboratory triggers

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution[a] 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[a] (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] 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.

*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

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.

[redacted]