Canakinumab to Reduce Deterioration of Cardiac and Respiratory Function in SARS-CoV2 Associated Acute Myocardial Injury and Hyperinflammation

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body Mass Index
BUN	blood urea nitrogen
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulation
CK	creatinine kinase
CK-MB	creatinine kinase MB
COAR	Clinical Operations, Analytics & Regions
COVID-19	coronavirus disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CTC	Common Toxicity Criteria
CTRD	Clinical Trial Results Database
CV	coefficient of variation
DMC	Data Monitoring Committee
EC	Ethics committee
Echo	Echocardiogram
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
eSAE	Electronic Serious Adverse Event
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	hour
HIV	human immunodeficiency virus
Hs-TnT	High-sensitivity troponin T
IL-6	Interleukin-6
i.v.	intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal

LLQ	lower limit of quantification
MABEL	minimum anticipated biological effect level
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MI	myocardial infarction
mL	milliliter(s)
ml	milliliter(s)
MRSD	maximum recommended starting dose
NT-proBNP	N-terminal pro-brain natriuretic peptide
o.d.	once a day
p.o.	oral
PD	pharmacodynamic(s)
RBC	red blood cell(s)
RDC	Remote Data Capture
REB	Research Ethics Board
s.c.	subcutaneous
SAE	serious adverse event
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	tuberculosis
TBL	total bilirubin
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization

1 Introduction

1.1 Background

In December 2019, a novel coronavirus (SARS-CoV2) resulted in an outbreak of pneumonia in Wuhan, China (coronavirus disease 2019, COVID-19) which has subsequently spread rapidly and resulted in a worldwide pandemic. The case fatality rate was initially reported ~2.3% (1), though a more recent study suggested a case fatality rate of 7.2% (2), and given the expected burden of disease, effective treatments are urgently required.

Even though the predominant manifestations are respiratory symptoms, concomitant cardiovascular complications result in substantial morbidity and mortality (3). Among an initial 179 patients with COVID-19 from Wuhan, 15 (8.4%) had acute cardiac injury syndrome, defined as abnormal serum cardiac markers or new electrocardiographic or echocardiographic abnormalities (4-6). In 49 patients admitted to the intensive care unit, 12 (24.4%) had acute cardiac injury. A separate study of 150 patients with COVID-19, including 68 deaths, demonstrated that the cause of death was related to myocardial damage in 27 patients (39.7%). In addition, cardiac troponin was higher in patients who died (30.3 vs 3.5 pg/mL, $p < 0.001$) (7). Another study of 50 patients reported in-hospital death only in the 18 patients with abnormal NT-proBNP (8). In a study of 113 patients who died and 161 patients who recovered from COVID-19, deceased patients had higher high-sensitivity troponin I (40.8 versus 3.3 pg/mL), NT-proBNP (800 versus 72 pg/mL), and CRP (113.0 versus 26.2 mg/L)(9).

Furthermore, in an initial US experience of 21 ICU patients who were COVID-19 positive, 7 developed cardiomyopathy, defined as a decrease in left ventricular systolic function without a past history of systolic dysfunction and clinical signs of cardiogenic shock(10). Moreover, in another study of 416 patients, 82 (19.7%) developed acute cardiac injury. These patients had higher levels of C reactive protein, were more likely to require mechanical ventilation and ARDS, and had a 51.2% mortality (11).

In patients who succumb to COVID-19, the troponin may continue to rise throughout the illness, a pattern distinct from the typical rise and fall after an ischemic insult (11). In some patients, this troponin elevation goes beyond what is typically observed in Type II MIs (12). Importantly, patients with elevated troponins have higher levels of C-reactive proteins (CRPs). The increases in troponin and CRP appear to parallel each other, and the overall correlation is similar in magnitude to the correlation between troponin and N-terminal pro-brain natriuretic peptides. These observations suggest that some patients may develop a hyperinflammatory state that perpetuates the non-ischemic myocardial injury.

Importantly, even though the current management of COVID-19 is supportive, morbidity and mortality may be driven by hyperinflammation in patients with severe COVID-19 infection (13). Hyperinflammation may progress to secondary hemophagocytic lymphohistiocystosis and resultant fatal hypercytokinemia with multiorgan failure. In this inflammatory state, immunosuppression may improve outcomes. In fact, in a subgroup analysis of a randomized controlled trial, patients with sepsis and organ dysfunction or hyperinflammation had improved survival with IL-1 receptor antagonism (14-15). Of note, in sepsis, IL-1 receptor antagonism has not been associated with adverse events, even at high doses (16).
Canakinumab is a fully human monoclonal antibody targeting IL-1β that has anti-inflammatory effects and is approved to treat auto-inflammatory diseases such as cryopyrin-

associated periodic syndromes and Familial Mediterranean Fever (17, 18). Canakinumab has been approved at a dose of 300 mg SC, and in clinical trials, doses of 600 mg SC have been safely tolerated (19). In the CANTOS trial, a randomized double-blind trial in autoinflammatory atherosclerotic disease, over 2000 patients received the 300 mg dose of canakinumab. Importantly, IL-1β drives the IL-6 pathway, and preliminary evidence of IL-6 antagonism in severe or critical COVID-19 disease has shown promise (20). Given the importance of myocardial dysfunction in the death of patients with COVID-19, the likely role of hyperinflammation, and the proven efficacy of canakinumab in autoinflammatory cardiovascular disease, we aim to identify high risk patients with acute myocardial injury related to COVID-19 and assess whether immunosuppressive treatment with canakinumab prevents further myocardial damage and heart as well as respiratory failure.

1.2 Purpose

The purpose of this prospective, Phase 2, single center, blinded, randomized controlled study is to demonstrate as a proof of concept that early treatment with canakinumab prevents progressive heart and respiratory failure in patients with COVID-19 infection. These results will lead to and inform a Phase III randomized placebo-controlled trial.

2 Objectives and endpoints

Primary Objective

To demonstrate that early treatment with canakinumab prevents progressive respiratory and heart failure in patients with SARS-CoV2 associated acute myocardial injury and hyperinflammation.

Secondary Objectives

- To evaluate in-hospital and overall mortality rates
- To evaluate progression of myocardial damage
- To evaluate progression of cardiogenic shock requiring mechanical circulatory support
- To evaluate the length of hospitalization
- To evaluate safety of canakinumab

Primary Endpoint

The primary end-point is the time to clinical improvement up to day 14, defined as the time in days from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever occurs first.

The ordinal scale consists of the following:

1. Not hospitalized with resumption of normal activities
2. Not hospitalized but unable to resume normal activities
3. Hospitalized, not requiring supplemental oxygen
4. Hospitalized, requiring supplemental oxygen
5. Hospitalized, requiring nasal high-flow oxygen, non-invasive mechanical ventilation or both
6. Hospitalized, requiring ECMO, invasive mechanical ventilation, or both
7. Death

Secondary Endpoint

The secondary end-point is mortality at day 28.

Exploratory Endpoints

- Need for mechanical ventilation in non-intubated patients
- Duration of mechanical ventilation in intubated patients
- Clinical status using the ordinal scale at day 7, day 14, day 21, and day 28:
  1. Not hospitalized with resumption of normal activities
  2. Not hospitalized but unable to resume normal activities
  3. Hospitalized, not requiring supplemental oxygen
  4. Hospitalized, requiring supplemental oxygen
  5. Hospitalized, requiring nasal high-flow oxygen, non-invasive mechanical ventilation or both
  6. Hospitalized, requiring ECMO, invasive mechanical ventilation, or both
  7. Death
- In-hospital and overall mortality at day 90 and day 150
- Length of intensive care unit (ICU) and total hospitalization stay
- Need for escalation to mechanical circulatory support (IABP, Impella, VA ECMO)
- Worst value for PaO2/FiO2 (or SaO2/FiO2 if PaO2 unavailable) at day 3, day 5, day 7, day 14, day 21, day 28, or until discharge
- Change in SOFA score at day 7, day 14, day 21, and day 28, or until discharge
- The time to peak in troponin
- Rate of decline of troponin after peak
- Time to peak c-reactive protein and subsequent rate of decline

- Time to peak ferritin levels and subsequent rate of decline
- Time to peak IL-6 levels and subsequent rate of decline
- Change in left ventricular ejection fraction from baseline to day 14 if still hospitalized and at day 90 if feasible
- Change in NT-proBNP from baseline to day 14 if still hospitalized and at 90 days if feasible
- Time to negative SARS-CoV2 RNA levels in oropharyngeal or nasopharyngeal samples

3 Study design

This is a prospective, Phase 2, single center, blinded randomized-controlled study designed as a proof of concept to demonstrate that early treatment with canakinumab prevents progressive heart and respiratory failure in patients with COVID 19 infection, myocardial injury and hyperinflammation. These results will lead to a Phase III randomized placebo-controlled trial.

Enrollment: The study will be performed in approximately 7 months total, starting from the first patient enrolled with enrollment expected to complete within 2 months.

Follow-up period: The follow-up period is 5 months for each patient enrolled.

Study completion: The end of the study, including statistical analysis and drafting of the final report is expected within 1 month from the last patient enrolled.

A total of 45 patients will be randomized using a 1:1:1 allocation ratio: 15 subjects will receive 600 mg intravenous canakinumab (8 mg/kg if </= 40 kg), 15 subjects will receive 300 mg intravenous canakinumab (4 mg/kg if </= 40 kg), and 15 patients will receive placebo infusion. The investigator, clinical team, and subject will be blinded to treatment assignment. Randomization will be stratified on whether or not the patient is intubated at the time of enrollment.

4 Rationale

4.1 Rationale for study design

We aim to identify high risk patients with acute myocardial injury related to COVID-19 and assess whether immunosuppressive treatment with canakinumab prevents further respiratory and heart failure.

4.1.1 Rationale for choice of background therapy

Given the importance of myocardial dysfunction in the death of patients with COVID-19, the likely role of hyperinflammation, and the proven efficacy of canakinumab in autoinflammatory cardiovascular disease, it was selected for further study in this patient population.

4.2 Rationale for dose/regimen and duration of treatment

Canakinumab is a fully human monoclonal antibody targeting IL-1β that has anti-inflammatory effects and is approved to treat auto-inflammatory diseases such as cryopyrin-associated

periodic syndromes and Familial Mediterranean Fever (17, 18). Promising immune treatments for cardiac disease also target autoinflammation, a process driven by endogenous danger signals and perpetuated by inflammasome-induced cytokine production. Canakinumab has previously demonstrated efficacy in inflammatory atherosclerotic disease (17). Canakinumab has been approved at a dose of 300 mg SC, and in clinical trials, doses of 600 mg SC have been safely tolerated (19).Importantly, IL-1β is the central cytokine in the inflammasome pathway and also drives the IL-6 pathway, and preliminary evidence of IL-6 antagonism in severe or critical COVID-19 disease has shown promise (20).

4.3 Risks and benefits

Interleukin-1 blockade may interfere with immune response to infections. Treatment with medications that work through inhibition of IL-1 has been associated with an increased risk of serious infections, particularly if used for a longer duration to treat a chronic disease.

The impact of treatment with anti-interleukin-1 (IL-1) therapy on the development of malignancies is not known. However, treatment with immunosuppressants, may result in an increase in the risk of malignancies.

Hypersensitivity reactions have been reported. During clinical trials, no anaphylactic reactions have been reported. It should be recognized that symptoms of the underlying disease being treated may be similar to symptoms of hypersensitivity.

In general, the risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, as well as periodic review of all safety data by an independent data monitoring committee (DMC).

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

The benefit a patient might have by participating in the study is the close monitoring of their condition and optimization of treatment of known risk factors during the full duration of the study.

5 Population

The study will enroll patients suffering from acute myocardial injury from SARS-CoV2 AND clinical and biological markers of systemic hyperinflammatory syndrome. The study will include patients hospitalized due to COVID-19 infection. The majority of these patients will likely have severe pneumonia, defined as tachypnea, severe respiratory distress, or SpO_2 </= 93% on room air. However, because initial acute cardiac injury in the absence of severe pneumonia has been reported, severe pneumonia is not required for inclusion.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.

2. Hospitalized due to COVID-19 infection
3. Documented SARS-CoV2 acute myocardial injury: Defined as upper respiratory tract specimen positive for COVID-19 AND troponin greater than 99th percentile upper reference range without signs or symptoms of acute myocardial ischemia
4. NT-proBNP or BNP greater than upper reference limit
5. Receiving current standard therapy
6. C-reactive protein (CRP) > 50 mg/L

5.2 Exclusion criteria

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

1. Alternative explanation for acute cardiac injury (Type I or Type II MI according to 4th Universal Definition of Myocardial Infarction, which in addition to a rise and fall of tropnonin above the 99th percentile upper reference limit, includes symptoms of acute myocardial ischemia, new ischemic ECG changes, development of pathologic Q waves, and imaging evidence of damage in a pattern consistent with an ischemic etiology)
2. Chronic Systolic Heart Failure with EF<35%
3. Age < 18 years-old
4. Uncontrolled systemic bacterial or fungal infection
5. Concomitant viral infection (e.g., Influenza or other respiratory virus)
6. Pregnant. Breast-feeding women are eligible with the decision to continue or discontinue breast-feeding during therapy taking into account the risk of infant exposure, the benefits of breast-feeding to the infant, and benefits of treatment to the mother.
7. On mechanical circulatory support
8. On mechanical ventilation for greater than 48 hours
9. Resuscitated cardiac arrest
10. Has a known hypersensitivity to canakinumab or any of its excipients
11. Neutrophil count <1000/mm3
12. Has a history of myeloproliferative disorder or active malignancy receiving chemotherapy
13. Known active tuberculosis or history of incompletely treated tuberculosis
14. Current treatment with immunosuppressive agents
15. Chronic prednisone use >10 mg/daily (for more than 3 weeks prior to admission)
16. Has a history of solid-organ or bone marrow transplant
17. Severe pre-existing liver disease with clinically significant portal hypertension
18. End-stage renal disease on chronic renal replacement therapy
19. Enrollment in another investigational study using immunosuppressive therapy
20. In the opinion of the investigator and clinical team, should not participate in the study
21. If male and sexually active, must have documented vasectomy or must practice birth control and not donate sperm during the study and for 3 months after study drug administration.

22. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of investigational drug. Such methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

6 Treatment

A total of 45 patients will be enrolled: 15 subjects will receive 600 mg intravenous canakinumab (8 mg/kg if </= 40 kg), 15 subjects will receive 300 mg intravenous canakinmab (4 mg/kg if </= 40 kg), and 15 patients will receive placebo infusion. Canakinumab or placebo will be dosed in 250 mL of 5% dextrose infused IV over 2 hours. No patient will receive more than one dose.

6.1 Study treatment

6.1.1 Investigational and control drugs

For investigation: 300 mg or 600 mg liquid canakinumab will be placed in 250 mL D5%W (dextrose 5%) and infused over 2 hours.

For placebo: 250 mL D5%W (dextrose 5%) will be infused over 2 hours.

6.1.2 Additional study treatments

No additional treatment beyond investigational drug are included in this trial.

6.1.3 Treatment arms/group

Eligible subjects will be randomized at the baseline visit.

6.1.4 Concomitant therapy

Medication classification used by the subject prior to randomization will be recorded in the eCRF pages.

Concomitant medications to track include: antipyretics, antibiotics related to secondary infections, anti-virals related to Covid-19, corticosteroids and other immunosuppressives. Other concomitant medications will be recorded at baseline and daily thereafter until Day 7, at Day 14, Day 21 and Day 28.

6.1.5 Prohibited medication

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving canakinumab. Therefore, live vaccines should not be given concurrently.

Prohibited medications include any cell-depleting biological therapies (e.g., anti-CD20) within 12 months prior to Day 0; or previous treatment with noncell-depleting biological therapies (such as anti-tumor necrosis factor [TNF], anakinra, anti-Interleukin [IL]-6 receptor [e.g. tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer) prior to screening, treatment with alkylating agents within 12 weeks prior to screening, intramuscular, receipt of live (attenuated) vaccine within the 4 weeks before Day 0, treatment with cyclosporine A, azathioprine, cyclophosphamide, or mycophenolate mofetil (MMF) within 4 weeks of screening.

Permitted concomitant therapy requiring caution and/or action:

TNF-Blocker and IL-1 Blocking Agent

An increased incidence of serious infections and an increased risk of neutropenia have been associated with administration of another IL-1 blocker in combination with TNF inhibitors in another patient population. Treatment with TNF-blocker within 8 weeks (or 5 half-lives, whichever is longer) is prohibited. More remote treatment with TNF-blockers is allow but requires caution, especially for neutropenia and infections, as noted**.**

Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, such as canakinumab, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin). Upon initiation of canakinumab, in patients being treated with these

types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

6.1.6 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available.

6.1.7 Treatment assignment, randomization

After meeting all inclusion/exclusion criteria and obtaining informed consent, patients will be randomized using a 1:1:1 allocation ratio to one of the three treatment groups. Randomization will be centralized through REDcap Cloud. Randomization will be stratified on whether or not the patient is intubated at the time of enrollment.

6.2 Treatment blinding

Subjects, investigator staff, persons performing the assessments, and the clinical trial team will be blinded to treatment. Only the Research Pharmacist and members of the Data Safety Monitoring Board will have access to the treatment assignments. If the clinical team decides that unblinding the patient is essential for subsequent significant clinical management, then the patient may be unblinded after discussion between the clinical team and the Principal Investigator, Paul Cremer.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described in the pharmacy manual.

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

6.3.1 Handling of study treatment and additional treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the pharmacy manual. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log.

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

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB -approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject 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 subject source documents.

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

A copy of the approved version of all consent forms will be kept by the Sponsor/Investigator. Visit schedule and assessments

The assessment schedule lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed.

7.1 Visit schedule and assessments

The assessment schedule lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed.

Table 7-1 Assessment Schedule*

Activity	Study Day [a]														
	-3 to 0 [b]	0	1	2	3	4	5	6	7	14* [c]	21* [c]	28*[c]	90	150	Unscheduled [d]
Informed consent	X														
Demographics	X														
Medical history[α]	X														
Eligibility	X														
Physical exam	X														X
Vital signs	X	X	X		X		X	X	X	X	X	X	X		X
Body Temperature (Celsius)	X	X	X	X	X	X	X	X	X	X	X	X			X
Body weight	X														
Height	X														
Medications	X	X	X	X	X	X	X	X	X	X	X	X			
Electrocardiogram	X									X			X		X
Chest imaging findings(chest X-Ray or CT) [β]	X														X
Echocardiogram	X									X			X		
Clinical assessment (7category scale)[a]	X	X	X	X	X	X	X	X	X	X	X	X			X
2019-nCoV test[γ]	X								X	X	X	X			X
Respiratory Virus Panel	X														
Troponin	X	X	X	X	X	X	X	X	X	X	X	X			X
NT-proBNP/BNP	X	X							X	X	X	X			X
Creatinine kinase (CK)	X	X	X	X	X	X	X	X	X	X	X	X			X
Creatinine kinase MB (CK-MB)	X	X	X	X	X	X	X	X	X	X	X	X			X
CRP	X	X	X	X	X	X	X	X	X	X	X	X			X
LDH [e]	X	X	X	X	X	X	X	X	X	X	X	X			X
D-Dimer [e]	X	X	X	X	X	X	X	X	X	X	X	X			X
Ferritin [e]	X	X	X	X	X	X	X	X	X	X	X	X			X
Interleukin 6 (IL-6) [e]	X	X			X				X	X	X	X			
Mechanical ventilation assessment	X	X	X		X		X		X	X	X	X			X

Respiratory parameters [g]	X	X	X		X		X		X	X	X	X			X
Viral Serology (inc. anti-2019-nCoV)	X									X		X			X
TB screening [h]	X														
HIV antibody [h]	X														
Hepatitis profile (Hepatitis B sAg, sAb, cAb; Hepatitis C Ab) [h]	X														
Pregnancy test [i]	X														
Hematology (CBC + diff)	X				X				X			X			X
Coagulation (PT, PTT, INR)	X														
Chemistry (lytes, BUN, glucose, CR)	X				X				X			X			X
Liver profile (AST, ALT, Alb, AlkP, Tbili, Dbili)	X				X				X			X			X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications [l]	X	X	X	X	X	X	X	X	X	X	X	X			X
Assessment of survival (day of death if occurs)	X	X	X	X	X	X	X	X	X	X	X	X	X	x	
Canakinumab/placebo administration		X													

*Given resource limitation related to COVID-19, all laboratory testing is considered standard of care, though as possible, certain tests that are not considered standard of care may be obtained for research. If the laboratory tests in the schedule of activities are obtained, they will be documented accordingly. If laboratory tests cannot be obtained for other reasons, such as requiring extra use of personal protective equipment, unnecessary exposure to healthcare personnel, or safety issues related to obtaining and processing samples, these will not be considered a protocol deviation. Visits at 14, 21, 28, 90 and 150 days may happen in-person or telehealth (labs not obtained if telehealth).

α The medical history must document the onset of symptoms as the time from onset of symptoms to enrollments will be documented. The reason for admission will also be documented.

β Chest imaging findings must document unilateral or bilateral infiltrates.

γ Nasopharyngeal or oropharyngeal swabs for SARS-CoV2 RNA levels will be performed until negative or discharge. Sampling will include both nostrils, or repeat sampling will include the same nostril if only one nostril is used.

a Study visits are planned for hospitalized patients only; planned activities that fall on study days that occur after the patient is discharged will not be done. **Assessments with the ordinal scale used for the primary outcome will be completed daily through Day 14 until clinical improvement, hospital discharge, or death.**

b Screening activities can occur from -3 and 0 days before enrollment except for Covid-19 testing, which can occur between -5 and 0 days before enrollment.

c For hospitalized patients, this visit will include the activities listed. For patients who have been discharged, visits will be conducted by phone but will not include any laboratory tests.
d An unscheduled visit is planned to occur on the day of discharge if the patient is discharged before Day 28; in which case this will serve as an early termination visit. If patient is discharged the visit on Study Day 28 will be done by telephone call follow-up and lab tests will not be performed. May also be used for adverse event assessments.
e Collect at least baseline and at least weekly thereafter.
g Includes FiO2 (degree of supplemental oxygen), SpO2, Respiratory rate and presence of respiratory distress, note if ventilated or not, if yes collect PEEP. For FiO2, SpO2, and PEEP, best and worst of daily value. Calculate P to F ratio best and worst for each day; proning; neuromuscular blockade; veno-venous or veno-arterial ECMO.
h Done at Investigator's discretion; not expected to be used for decision to treat; not a mandatory test.
i Females of child-bearing potential only, urine or serum at investigator's discretion.
J Includes complete blood count (CBC) and differential at screening and CBC on subsequent indicated days.

l Prohibited medications include any cell-depleting biological therapies (e.g., anti-CD20) within 12 months prior to Day 0; or previous treatment with noncell-depleting biological therapies (such as anti-tumor necrosis factor [TNF], anakinra, anti-Interleukin [IL]-6 receptor [e.g. tocilizumab], or abatacept) within 8 weeks (or 5 half-lives, whichever is longer) prior to screening, treatment with alkylating agents within 12 weeks prior to screening, intramuscular, receipt of live (attenuated) vaccine within the 4 weeks before Day 0, treatment with cyclosporine A, azathioprine, cyclophosphamide, or mycophenolate mofetil (MMF) within 4 weeks of screening

Concomitant medications to track include: antipyretics, anti-infectives related to COVID-19, other antibiotics, corticosteroids and other immunosuppressives. The timing of administration of these medications must be recorded. Other concomitant medications recorded at baseline day 0 and maximum dose.

7.2 Subject demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all subjects. The number of days between onset of COVID-19 symptoms and initiation of treatment will be recorded in all patients.

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.

7.2.1 Laboratory evaluations

Pre-treatment screening:

- Complete blood count (CBC), serum biochemical tests (including renal and liver function), albumin, total protein, coagulation profile, D-dimer, fibrinogen, troponin, CK, CK-MB, NT-proBNP or BNP, LDH, CRP, serum ferritin, IL-6, quantiferon, HBV, HCV, HIV serology, urine or serum pregnancy test.

On-treatment measurements (as noted in the schedule of activities):

- Complete blood count (CBC), serum biochemical tests (including renal and liver function), albumin, total protein, coagulation profile, D-dimer, 5th generation Roche high-sensitivity troponin T, CK, CK-MB, LDH, CRP, serum ferritin, IL-6

7.2.2 Electrocardiogram (ECG)

A baseline electrocardiogram with assessment for acute or prior myocardial ischemia or infarction will be obtained.

Follow-up ECG will similarly be obtained at day 14 if the patient is still hospitalized or at day 90 if feasible.

7.2.3 Echocardiogram (Echo)

A baseline echocardiogram with assessment of left ventricular ejection fraction will be completed after onset of COVID-19 symptoms, and as close as possible prior to canakinumab or placebo infusion.

Follow-up echocardiogram with assessment of left ventricular ejection fraction will be collected at day 14 if the patient is still hospitalized and at day 90 if feasible.

7.2.4 Pregnancy assessments

All pre-menopausal women who are not surgically sterile will have a urine or serum pregnancy test performed at the screening visit. Pregnancy testing is not required for post-menopausal women.

Clinically significant abnormalities must be recorded on the relevant section of the CRFs capturing medical history/Current medical conditions/AE as appropriate.

8 Study discontinuation and completion

8.1 Discontinuation

8.1.1 Discontinuation of study treatment

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

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being. After study treatment discontinuation, patient should remain in the study, unless he/she withdraws consent (Section 9.1.2), preferably in writing.

Study treatment must be discontinued under the following circumstances

- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment
- Any situation in which study participation might result in a safety risk to the subject
- Any laboratory abnormalities that in the judgment of the investigator prevents the subject from continuing study drug administration

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

Subjects 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. Where possible, they should return for the assessments indicated in the assessment schedule, **understanding that this is often not be possible with an ongoing COVID-19 pandemic**. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letter) should be made to contact the subject/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 subject cannot or is unwilling to attend any visit(s), including the planned telehealth visits, the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule. Patient’s vital status can also be verified by the study site upon contact with patient’s primary care physician or other sources according to local rules and regulations.

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

8.1.1.1 Replacement policy

Subjects who are enrolled but not randomized will be replaced. Subjects who withdrawal consent before receiving study infusion will also be replaced.

8.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore

And

- Does not allow further collection of personal data

It is encouraged that patient provides withdrawal of consent in writing.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information. Patient's vital status can be verified upon contact with patient's primary care physician or other sources according to local rules and regulations.

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 subject are not allowed unless safety findings require communicating or follow-up.

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

Cleveland Clinic will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law:

8.1.3 Lost to follow-up

For subjects 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 subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until the end of the study while due diligence has been completed.

8.1.4 Early study termination by the sponsor

The study can be terminated by the Sponsor/Investigator at any time. Reasons for early termination:

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

In taking the decision to terminate, the Sponsor/Investigator will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

8.2 Study completion and post-study treatment

Study completion is defined as when the last subject 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.

9 Safety monitoring and reporting

9.1 Definition of adverse events and reporting requirements

9.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject 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 subject and identifying adverse events.

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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events CRF 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. The 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 subject

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

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

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn
- its outcome
    a. not recovered/not resolved;
    b. recovered/resolved;
    c. recovering/resolving,
    d. recovered/resolved with sequelae;
    e. fatal; or unknown.

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

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 for at least 16 weeks following the last dose of study treatment.

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 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 subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

9.1.2 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 subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (coronary heart disease, cerebrovascular disease or peripheral vascular disease).
    - 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 subject'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 subject 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 subject 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.

All 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 (Table 10-1).

9.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until the last study visit must be reported to the Investigator within 24 hours of learning of its occurrence.

Sponsor/investigator is responsible for evaluating all safety information available, and notify FDA and all investigators in an IND safety report of potentially serious risks from this clinical trial or any other source as soon as possible but not later than 15 calendar days after the sponsor/investigator receives the safety information and determines that the information qualifies for reporting.

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

Suspected and Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to FDA.

Any SAEs experienced after the Completion Study should only be reported to sponsor/investigator

9.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Sponsor/Investigator 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. Newborn will be followed up just until birth according to guidelines as there was nothing observed in any studies that would suggest a fetal development risk.

Any SAE experienced during pregnancy must be reported.

9.1.5 Reporting of study treatment errors

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

9.1.6 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor/investigator whether to continue, modify or terminate a trial.

The Data Monitoring Committee will make an assessment after every administration of study drug for the first 6 patients using all available data in the patient's medical record. Summary reports will be provided to the DMC after the first six subjects have been reviewed, after 12 subjects have been reviewed, and after every 6 subsequent patients. The DMC will include representatives from Pulmonary/Critical Care, Rheumatology, Infectious Disease, and Cardiology.

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

Schedule of Safety Assessments:

	Study Day														
Activity	-3 to 0	0	1	2	3	4	5	6	7	14	21	28	90	150	Unscheduled
Vital signs	X	X	X						X	X	X	X	X		X
Medications	X	X	X						X	X	X	X			
Respiratory parameters	X	X	X						X	X	X	X			X
Hypersensitivity reaction			X	X	X	X	X	X	X						
Secondary infections	X	X	X						X	X	X	X	X	X	X
Hematology (CBC + diff: assessment for leukopenia, neutropenia, and thrombocytopenia)	X				X				X			X			X
Coagulation (PT, PTT, INR)	X														
Chemistry (lytes, BUN, glucose, CR)	X				X				X			X			X
Liver profile (AST, ALT, Alb, AlkP, Tbili, Dbili: assessment for drug-induced liver injury according to Hy's law)	X				X				X			X			X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	x	X

10 Data Collection and Database management

10.1 Data collection

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

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

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

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

10.2 Site monitoring

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. 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 subjects will be disclosed.

11 Data analysis and statistical methods

11.1 Analysis sets

All patients who provide informed consent, are randomized and receive study medication will be included in the analysis.

11.2 Subject demographics and other baseline characteristics

The number and percentage of patients who completed the study, who discontinued the study and the reason for discontinuation will be presented for all patients. The frequency (%) of patients with major protocol deviations as well as the criteria leading to data exclusion from analysis will be presented in separate tables, if applicable. Finally, the number of enrolled patients by site will be presented descriptively.

Baseline value is defined as the last non-missing assessment prior to the first dose of study drug unless specified otherwise.

Demographic and background characteristic variables will be summarized using descriptive summary statistics. Continuous variables will be summarized using n, mean, standard deviation, median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

11.3 Analysis of the primary endpoint and secondary endpoints

Based on prior reports of poor prognosis in patients who have SARS-CoV2 and an elevated troponin in terms of high likelihood of requiring mechanical ventilation, developing acute respiratory distress syndrome, and death, as well as low likelihood of demonstrating clinical improvement we estimate an event rate of 0.8 in the control group. However, estimates of efficacy of canakinumab in this patient population are not established. Therefore, no inferential statistics are planned *a priori*. The results from this pilot study will provide important data regarding effect size to inform feasibility of larger studies. The primary efficacy analysis will be on an intention-to-treat basis and include all patients who are randomized. The primary efficacy comparison will be between patients receiving canakinumab 600 mg IV versus placebo. The time to clinical improvement will be assessed daily until day 14, and for the purposes of the primary endpoint, failure to reach clinical improvement or death before day 14 considered as right-censored at day 14. Of note, we plan to analyze the primary end-point after all patients have reached day 14 to expeditiously inform whether a larger study should be undertaken. In addition to analysis of the entire cohort, we also planned to perform separate analyses of patients who are and who are not intubated at the time of randomization since these may represent distinction populations. As noted, as we do not plan inferential statistics, data for endpoints will be displayed as point estimates with 95% confidence intervals. None of these estimates or intervals should be regarded as definitive for treatment effect.

11.3.1 Adverse events

All information obtained on adverse events will be summarized in tabular format.

A subject with multiple adverse events of the same type is only counted once towards the total of that event.

All deaths and serious adverse events will be tabulated.

All AEs, deaths and serious adverse events will be provided in patient listings.

12 Ethical considerations and administrative procedures

12.1 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 US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures and any other written information to be provided to subjects. Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted on Clinicaltrials.gov

13 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 subjects should be administered as deemed necessary on a case by case basis. 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.

13.1 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 subject 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 subject 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 at the study site should be informed according to local regulations.

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