Clinical Study Protocol

Study Title:	**Study to evaLuate the EfficAcy and Safety of CardiolRx™ in PatieNts with COVID-19 and Cardiovascular DisEase or Risk Factors** A double-blind, placebo-controlled trial (**LANCER**)
Sponsor:	Cardiol Therapeutics Inc. 2265 Upper Middle Road East Suite 602 Oakville, ON, L6H 0G5, Canada
Protocol Prepared by:	Cardiol Therapeutics Inc.
Document type:	Clinical Study Protocol Amendment
Protocol number:	CARDIOL 100-03
Date of original Study Protocol:	October 20, 2020, version 1.16 and May 12, 2021, version 1.17 (Brazil)
Amendment number:	3
Release date:	September 23, 2021

Signature Page for Sponsor

Study to evaluate the Efficacy and Safety of CardiolRx™ in Patients with COVID-19 and Cardiovascular Disease or Risk Factors: A double-blind, placebo-controlled trial (LANCER)

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Title:	**Study to evaluate the Efficacy and Safety of CardiolRx™ in Patients with COVID-19 and Cardiovascular Disease or Risk Factors** A double-blind, placebo-controlled trial (LANCER)
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I have read this protocol amendment and the Investigator Brochure and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Investigator Name Please print	Signature	Date Please Print

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1 STUDY SYNOPSIS

Protocol Title	**Study to evaluate the Efficacy and Safety of CardiolRx™ in Patients with COVID-19 and Cardiovascular Disease or Risk Factors** A double-blind, placebo-controlled Phase II/III Study (LANCER)
Diagnosis	Non-critical patients, hospitalized for COVID-19 with a prior history of cardiovascular disease (CVD) and/or at least one risk factor for CVD
Inclusion Criteria	1. Males and females 18 years of age or older 2. Hospitalized for COVID-19 with most recent test positive*; not receiving, or likely to receive invasive mechanical ventilation within the next 24 hours 3. Prior history of at least one of: i) CVD [cardiovascular (CV), cerebrovascular or peripheral vascular diagnoses], ii) Age > 64, iii) Diabetes (DM), iv) Hypertension (HTN), v) Abnormal serum lipids, vi) Obesity (BMI≥30 or waist circumference >102 cm [40”] for men and >88 cm [35”] for women), vii) Current smoker * Must be polymerase chain reaction (PCR) test.
Exclusion Criteria	1. Patients who have received vasopressors, extracorporeal membrane oxygenation and mechanical ventilation within last 30 days 2. Background of cardiac transplant surgery 3. Implanted defibrillator (ICD) in the last month 4. Implanted left-ventricular assist device (LVAD) 5. Acute coronary syndrome (ACS) within 30 days 6. Percutaneous coronary intervention (PCI) within 30 days 7. Receiving any immuno-suppressive agent other than dexamethasone 8. History of QTc interval prolongation 9. QTc interval > 500 msec (see section 9.2.3 for bundle branch block [BBB] correction)

10. Treated with strong inducers of CYP3A4 or CYP2C19, as listed in Appendix 17.7
11. Chronic renal failure, determined as eGFR < 30 ml/min
12. Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 times the upper limit of normal (ULN) or ALT or AST >3x ULN plus bilirubin >2x ULN
13. Bacterial sepsis, defined as documented bacteremia at the time of presentation or other active bacterial infection
14. Current participation in any research study involving investigational drugs or devices with the exception of dexamethasone, remdesivir, Baricitinib plus remdesivir as well as convalescent plasma and monoclonal antibodies, or any other therapy approved under emergency use in the region for treatment of COVID-19
15. Inability or unwillingness to give informed consent
16. Ongoing drug, alcohol or cannabis abuse
17. Women who are pregnant or breastfeeding
18. Any factor, which would make it unlikely that the patient can comply with the study procedures
19. Hemoglobin <8.5 gm/dL
20. Leukocyte count < 3000/ mm^3
21. Platelets < 100,000 / mm^3
22. Current diagnosis of cancer, with the exception of non-melanoma skin cancer
23. Showing suicidal tendency as per the Columbia-Suicide Severity Rating Scale (C-SSRS) administered at screening
24. Any cannabinoid intake in the past month
25. Body weight > 170 kg

Primary Efficacy Objective

The primary objective of this study is to evaluate the effect of CardiolRx™ on prevention of cardiovascular and COVID-19 complications in patients hospitalized for COVID-19.

Primary Efficacy Endpoint

The primary composite endpoint in this study is to experience one of the following events during the first 28 days post randomization:

- All-cause mortality
- Requirement for ICU admission and/or ventilatory support due to COVID-19
- CV complications*:
  - heart failure (HF) or
  - Acute myocardial infarction (AMI) or

- myocarditis or
- new sustained or symptomatic arrhythmia or
- stroke

*see Appendix 17.8 for definitions

Secondary Efficacy Endpoints

- …Win Ratio of Ordinal Outcome Scale endpoint:
  1) not hospitalized and no limitations of activities;
  2) not hospitalized, with limitation of activities, home oxygen requirement, or both;
  3) hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care
  4) hospitalized, not requiring supplemental oxygen but requiring ongoing medical care
  5) hospitalized, requiring any supplemental oxygen;
  6) hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices;
  7) hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
  8) MI or stroke diagnosed since randomization
  9) death.

- Change in hs-troponin from baseline to peak elevation during the 28-day treatment period
- Change in TNF-alpha from baseline to peak elevation during the 28-day treatment period

Other Endpoints	- Percentage of patients developing any of the primary endpoint components within 60 days post randomization - CV mortality at 28 days post randomization - Percentage of patients requiring dialysis within 28 days post randomization - Win ratio of the Ordinal Outcome Scale endpoint within 60 days of randomization - Patient Impression of Change Questionnaire (PICQ) at Day 28 and at Day 60 - Development of severe lymphopenia, defined as < 1000 cells/ microliter within 28 days post randomization - Change in (elevation of) hs-troponin, NT-proBNP, D-dimer and in inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10) from baseline to Day 7 [area under the curve (AUC)] - Change from baseline to peak elevation of NT-proBNP, D-dimer and in inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10) during the 28-day treatment period - Change from baseline to peak elevation of lactate dehydrogenase (LDH) during the 28-day treatment period - Difference in cardiac magnetic resonance imaging (CMR) parameters between the two treatment groups after 4 weeks of study treatment (subset of patients at selected sites)
Primary Safety Objective	To evaluate the safety of CardiolRx™ in patients with COVID-19 infection
Primary Safety Endpoint	Number of serious adverse events (SAEs) and adverse events (AEs) during the 60-day study period in each group
Secondary Safety Endpoints:	Changes in C-SSRS, blood chemistry and hematology parameters (including lymphocyte count), ALT, AST, bilirubin, eGFR, creatinine, international normalized ratio (INR) as well as QTc interval
Number of Patients:	422 patients will be randomized (211 to CardiolRx™ and 211 to placebo)
Scheduled Duration of Study:	Estimated 9 months recruitment, 2 months follow-up, data cleaning 2 months and 2 months statistical analysis and reporting; If all timelines are met, the total duration of the study will be approx. 15 months.
Design & Methodology	Multi-center, double-blind, randomized, placebo-controlled, parallel group design. 1:1 randomization. Screening (Day 0-1): Patients hospitalized for COVID-19 will be screened. If patient consent can be obtained, baseline assessments will be carried out: Physical examination (including vital signs),

electrocardiogram (ECG) including QTc interval assessment, echocardiogram to measure left-ventricular ejection fraction (LVEF), chest X-ray, local laboratory (including complete blood count [CBC], Alanine aminotransferase [ALT]/ Aspartate aminotransferase [AST], alkaline phosphatase, bilirubin, creatinine/ estimated Glomerular filtration rate [eGFR], international normalized ratio [INR], serum pregnancy test [in women with child-bearing potential only], glucose, total cholesterol, lymphocyte count and lactate dehydrogenase [LDH]. A Columbia-Suicide severity rating scale (C-SSRS will also be completed). Frozen samples will be retained for central analysis of CardiolRx™ levels, high sensitivity troponin (hs-troponin), N-terminal pro b-type natriuretic peptide (NT-proBNP), D-dimer as well as inflammatory markers (high sensitivity C-reactive protein [hs-CRP], ferritin, tumor necrosis factor [TNF]-alpha, interleukin [IL]-1 beta, IL-6, IL-10).

If all eligibility criteria are met, the patient will be randomized to either CardiolRx™ or placebo. Randomization must be no later than 96 hours after hospital admission. Patients awaiting planned admission to hospital in an emergency room for less than 96 hours can be screened and enrolled into the trial.

Study treatment will be initiated in the evening of Day 1 after all baseline assessments have been completed and the patient is randomized.

Oral administration is as follows:

Study Day	**a.m. dose [mg/kg of body weight]** CardiolRx™ or placebo	**p.m. dose [mg/kg of body weight]** CardiolRx™ or placebo
1	N/A	2.5
2	2.5	2.5
3	2.5	5
4	5	5
5	5	7.5
6 - 28	7.5	7.5

Study medication must be taken with food.

If the next higher dose is not tolerated, the dose will be reduced to the previous tolerated dose. The highest tolerated dose will be administered until Day 28.

On Days 3, 5, and 7, an ECG will be recorded 5 hours post morning dose (time window 3.5 – 6 hours) with QTc intervals measured. If the QTc interval is >500 msec or an increase of > 60 msec from baseline is observed, the study medication must be stopped immediately.

In addition to prolongation of the QTc intervals, careful observation is required to detect other Adverse Drug Reactions (ADRs) and Drug-Drug Interactions (DDIs). Because CardiolRx™ may inhibit the metabolism of other drugs, new symptoms may represent toxicity from a concomitant medication that had previously been well tolerated. For more detailed discussion, see the Investigational Brochure (IB), section 6.3.

If the patient is discharged before Day 7, the assessments up to Day 7 will be carried out as out-patients or home visits. After Day 7, all remaining scheduled assessments will be carried out during out-patient visits.

After Day 7, assessments will be carried out on a weekly basis until Day 28.

Frozen samples will be retained for central analysis of CardiolRx™ levels, hs-troponin, NT-proBNP, D-dimer, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10) and additional parameters of interest every two days until Day 7 as well as on Day 28.

The assessments on Day 28 include the following: Physical examination (including vital signs), ECG recorded 5 hours post morning dose (time window 3.5 – 6 hours) for measurement of QTc interval, echocardiogram to measure LVEF, chest X-ray, local and central laboratory assessments. In addition, a C-SSRS will be completed and the patient will be asked to answer a PICQ. In a subset of patients at selected sites, a CMR assessment will be done as well (this will be scheduled for day 45 if not possible to obtain on day 28).

Further follow-up visits are scheduled for Day 45 and Day 60 post randomization. These include a clinical assessment (including vital signs) as well as the completion of the PICQ (PICQ on Day 60 only). Any changes in concomitant medications and (S)AEs will also be recorded.

Information regarding the Ordinal Outcome Scale will be collected at each visit.

Concomitant Treatments	Patients may be on standard of care (SOC) treatment(s) for all current conditions, as prescribed by their treating physician, including dexamethasone, remdesivir, baricitinib plus remdesivir, intravenous monoclonal antibody infusion (administered prior to admission), and convalescent plasma therapy, with the exception of cannabinoids and strong inducers of CYP3A4 and CYP2C19 (see Appendix 17.7).
Data Safety and Monitoring	The QTc intervals for the first 100 patients will be reviewed by the Data Safety and Monitoring Committee (DSMC) in an unblinded fashion. If QTc interval prolongation occurs more often in the active group, as compared to placebo, the DSMC will continue close monitoring of the QTc intervals. The DSMC will also review all safety events on an ongoing basis by treatment code and will conduct a formal (unblinded) interim analysis after approximately 50% of the patients have completed 28 days of study or terminated the study earlier, and will make recommendations to the Steering Committee on further conduct of the study following Stopping Guidelines in section 11.7 of this protocol. In addition, the DSMC has the right to recommend stopping the trial early for evidence of harm that was not pre-defined by a formal stopping rule.
Statistical Analysis	*Sample Size Estimation* Assuming that 19% of patients qualifying for the study in the placebo group would develop one or more primary outcomes, a treatment effect of lowering the event rate by 50% (i.e. only 9.5% of patients treated with CardiolRx™ would experience CV or COVID-19 complications), a two-sided alpha of 0.05 and 80% power, 211 patients per group (422 in total) would be required. Consideration will be given to adjust the sample size just before the formal interim analysis is carried out, should the observed event rate differ from the assumption above. Consideration will also be given to upgrading the Ordinal Outcome Scale first secondary endpoint to be the primary endpoint should the event rate of the current primary endpoint be significantly lower than the above assumption. This would be carried out in a blinded fashion. If the overall primary event rate is lower than (19 + 9.5)/2 = 14.25%, the sample size will be increased to preserve 80% power to detect a 50% relative reduction with a two-sided alpha of 0.05. *Statistical Analysis Approach:* *Primary efficacy analysis:* For the primary efficacy analysis, the proportions of subjects with at least one primary composite endpoint event will be compared using

Fisher's exact test. In addition, the 95% confidence interval for the proportion using exact (Clopper-Pearson) estimates will be provided. A secondary exploratory sensitivity analysis of the primary endpoint will compare time to the occurrence of the first primary event between the two groups using a Cox proportional hazards model. Kaplan-Meier plots for each treatment group will also be generated.

Secondary efficacy and safety analyses:

The first secondary efficacy analysis will be analyzed using the F-S test (Finkelstein and Schoenfeld 1999). This method compares each subject to every other subject in a pairwise manner following the ranking of the first secondary endpoint:

1) not hospitalized and no limitations of activities;
2) not hospitalized, with limitation of activities, home oxygen requirement, or both;
3) hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care
4) hospitalized, not requiring supplemental oxygen but requiring ongoing medical care
5) hospitalized, requiring any supplemental oxygen;
6) hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices;
7) hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
8) MI or stroke diagnosed since randomization
9) Death

The F-S test is based on the sum of 'scores' of subjects in the CardiolRx™ group. Where the score is 1, -1 or 0 according to whether the subject is the winner, the loser or tied, respectively, according to the hierarchy above.

In addition, the CardiolRx™ to placebo Win ratio (WR) will be calculated, as described by Pocock.(Pocock et al. 2012) For this statistic, every subject in the CardiolRx™ group is compared to every subject in the placebo group in a pairwise manner following the ranking of the first secondary efficacy endpoint. The WR is the number of pairs with CardiolRx™ subject 'wins' divided by the number of pairs with placebo subject 'wins'. The associated 95% CI will bebased on the F-S test statistic to ensure consistency between the CI and the F-S test. A 95%CI for the WR entirely above 1 indicates a better outcome in the CardiolRx™ group.

Changes in hs-troponin and TNF-alpha to peak elevation from baseline during the 28-day treatment period will be compared using an ANCOVA with baseline as covariate.

To control the family-wise Type I error rate, the Benjamini-Hochberg procedure (Benjamini and Hochberg 1995) will be applied.

For the other efficacy endpoint analyses, see section 11.2.3 of this protocol.

Descriptive statistics will be used to compare baseline characteristics between the two groups. Continuous variables will be expressed as mean ± standard deviation (SD) or as median and interquartile range (IQR); categorical variables will be expressed in counts with percentages.
The primary analyses will follow the intention-to-treat principle. Per-protocol secondary analyses may be considered, if appropriate.

Interim Analysis

A formal interim analysis will be carried out after approximately 50% of patients completed the 28-day assessment (or terminated the study early). The DSMC will make recommendations to the Steering Committee regarding the appropriateness of continuing the study following Stopping Guidelines in section 11.7 of this protocol.

2 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
ADR	Adverse drug reaction
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
API	Active pharmaceutical ingredient
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BNP	Brain natriuretic peptide
CAD	Coronary artery disease
CB	Canonical endocannabinoid receptors
CBC	Complete blood count
CBD	Cannabidiol
cGMP	Current good manufacturing practice
CMR	Cardiac magnetic resonance imaging
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CVD	Cardiovascular disease
CYP	Cytochromes P450
DDI	Drug-drug interaction
DIC	Disseminated intravascular coagulation (DIC)

Abbreviation	Definition
DM	Diabetes mellitus
DSMC	Data Safety and Monitoring Committee
eCRF	Electronic Case Report Form
ECV	Extracellular volume
eDCF	Electronic Data Clarification Form
eGFR	Estimated Glomerular filtration rate
GCP	Good Clinical Practices
GLS	Global longitudinal strain
GPR	G-protein-coupled receptors
HF	Heart failure
HR	Heart rate
hs-CRP	High sensitivity-C-reactive protein
hs-troponin	High sensitivity-troponin
HTN	Hypertension
HT1A	5-hydroxytryptamine (serotonin) receptor 1A
IB	Investigational Brochure
ICD	Implantable cardioverter defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IL	Interleukin
INR	International normalized ratio
IRB/REB	Institutional Review Board/Research Ethics Board
IQR	Interquartile range
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase

Abbreviation	Definition
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
LVAD	Left ventricular assist device
MCT	Medium-chain triglyceride
NT-proBNP	N-terminal pro b-type natriuretic peptide
PCI	Percutaneous coronary intervention
PCR	Polymerase chain reaction
PICQ	Patient impression of change questionnaire
PPAR	Peroxisome proliferator-activated receptor
RVEDV	Right ventricular end-diastolic volume
RVESV	Right ventricular end-systolic volume
SAE	Serious Adverse Event
SD	Standard deviation
SOC	Standard of Care
THC	Tetrahydrocannabinol
TNF	Tumor necrosis factor
TRP	Transient receptor potential
UGT	Uridine diphosphate glucuronosyl transferase
ULN	Upper limit of normal
WWCT	Worldwide Clinical Trials

3 BACKGROUND

3.1 Description of COVID-19

The COVID-19 pandemic is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).(Guo et al. 2020; Zhu et al. 2020) The disease was first recognized in China in late 2019 in the city of Wuhan (Guan et al. 2020). From there it rapidly spread throughout much of China, and subsequently much of the world. By June 30, 2020, there were more than 10 million cases reported worldwide with more than 500,000 deaths. In the USA, on this date, there were more than 2.5 million cases with approximately 125,000 deaths. For comparison, the numbers in Canada on the same date were 103 thousand cases with 8500 deaths. By any parameter, this is a very significant health issue that has, and continues to, tax the capacities of national health care systems.

The virus is very contagious (Zhang et al. 2020), spreading primarily through droplets emitted from an infected person when coughing or sneezing (R. T. Gandhi, Lynch, and del Rio 2020). For this reason, the major public health prevention techniques are social distancing and wearing masks. The virus has also been detected in stool although fecal-oral spread has not been identified (R. T. Gandhi, Lynch, and del Rio 2020). Neither has airborne spread been proven but there is increasing concern that it does occur. Unfortunately, the virus can also survive on hard surfaces for as much as 2-3 days (Kampf et al. 2020), and from there can contaminate hands with subsequent infection by touching the eyes, nose or mouth. Of significant worrisome epidemiologic significance is the observation that SARS-CoV-2 is also spread from asymptomatic persons (M. Gandhi, Yokoe, and Havlir 2020). A recent publication estimated that asymptomatic patients could make up to 40% to 45% of all COVID-19 cases; it is also suggested that such patients could potentially transmit virus for more than 14 days (Oran and Topol 2020). Although sampling (for diagnostic purposes) is usually from the naso-pharynx, samples from an infected person's oro-pharynx (R. T. Gandhi, Lynch, and del Rio 2020) or even saliva (Azzi et al. 2020) are frequently positive. The major point of entry into tissues seems to rely on the Angiotensin converting enzyme (ACE) II receptors which are particularly prominent in the alveolar cells of the lung (Hoffmann et al. 2020), although also common in cardiac and kidney cells. Experimentally, it has recently been shown that the SARS-CoV-2 virus can infect cardiomyocytes (produced by stem cell technology), raising the possibility that the virus might infect the heart muscle directly during the disease (Sharma et al. 2020). The virus binds to the ACE II receptor and enters the cell through a process of endocytosis (Hoffmann et al. 2020). The result of this process is a down-regulation of the ACE II receptor with resultant decrease in the conversion of Angiotensin II to Angiotensin 1-7; the increased levels of Angiotensin II cause increased vasoconstriction, and is pro-oxidant, pro-inflammatory, pro-proliferative and pro-fibrotic (Kuster et al. 2020). The diagnosis of COVID-19 is usually based on the detection of SARS-CoV-2 by means of PCR from a naso-pharyngeal sample (R. T. Gandhi, Lynch, and del Rio 2020).

3.2 Risk Factors for COVID-19

Other than exposure to an infected person, the most prominent risk factor for the development of the disease is age greater than 64 (R. T. Gandhi, Lynch, and del Rio 2020). However, other common risk factors for the development of the disease are the presence of pre-existing CVD or common risk factors for CVD. These include diabetes, obesity (BMI≥30), hypertension, abnormal serum lipids, chronic obstructive pulmonary disease and chronic renal failure (M. Gandhi, Yokoe, and Havlir 2020; Driggin et al. 2020; Rottoli et al. 2020)("CMS Medicare Claims and Encounter Data" 2020). Importantly, the presence of CVD increases the risk of poor outcomes, and particularly of developing CV complications (Driggin et al. 2020; Li et al. 2020; F. Zhou et al. 2020). It is now estimated that approximately 40% of deaths from COVID-19 are related to cardiovascular complications. Approximately 20% of patients develop myocardial injury (as reflected by release of troponin) and some develop frank myocarditis (F. Zhou et al. 2020; K. Liu et al. 2020),(Xu et al. 2020),(Szekely et al. 2020). Although uncommon, patients who develop myocarditis may go on to develop heart failure (HF) or even shock syndrome (Ruan et al. 2020). Importantly, recent evidence suggests that the virus infects the endothelial cells which also express the ACE II receptor (Varga et al. 2020). This endotheliitis may explain the impaired micro-circulation observed in different vascular beds, and raises the possible therapeutic benefit of treating the endothelial dysfunction with anti-inflammatory agents and anti-cytokine medications. Some COVID-19 patients develop ACS with myocardial infarction as reflected by electrocardiographic and enzyme changes. Such injury has been reported in 7 – 17% of hospitalized patients, and is more common in those admitted to the ICU (F. Zhou et al. 2020; P. Zhou et al. 2020). Arrhythmias are also common among patients with COVID-19 admitted to hospital (K. Liu et al. 2020; P. P. Liu et al. 2020).

3.3 The Clinical Course

Initially, COVID-19 is primarily a pulmonary disease but there are many other manifestations that are coming to light. The usual incubation period for COVID-19 averages 4-5 days but in some cases can extend to 11 to 14 days (Lauer et al. 2020). The early symptoms include a dry cough, fever in approximately 50% of patients (Guan et al. 2020) and then usually shortness of breath, which develops after 5-8 days and often signals worsening disease (R. T. Gandhi, Lynch, and del Rio 2020). Other symptoms include headache, myalgia, tiredness and in some cases, loss of smell and taste (Giacomelli et al. 2020; R. T. Gandhi, Lynch, and del Rio 2020). Some patients (particularly younger ones) may develop a skin rash. In this regard, reports have appeared of redness and swelling in the toes that become tender but do not ulcerate; this is being referred to as COVID Toes (P. P. Liu et al. 2020; Freeman 2020). But differing presentations are being recognized. In a more recent publication from the Evelina London Children's Hospital, London, UK, Riphagen et al. reported a series of 8 children admitted over 10 days in mid-April with what has been termed a hyper-inflammatory syndrome with many similarities to Kawasaki Disease (Riphagen et al. 2020). All of these children progressed to develop shock syndrome requiring vasopressor therapy. Interestingly none had particular respiratory symptoms. One patient developed a giant coronary aneurysm and one child developed serious arrhythmia, developed shock and after

therapy with extracorporeal membrane oxygenation died from a large cerebrovascular infarction. Since that report, more than 100 similar cases have been reported in the city of New York (Verdoni et al. 2020).

Once shortness of breath develops, the disease can follow a number of courses. Some patients will stabilize and then gradually improve while remaining at home. Others will develop hypoxemia on room air and usually require hospitalization. Some such patients deteriorate further and require intensive care (ICU). In early reports from China, approximately 80% of COVID-19 positive patents had mild disease and recovered at home (Wu and McGoogan 2020), approximately 15% developed more serious disease and required hospitalization, many of whom were treated with supplemental oxygen. The remaining 5% developed critical disease and required ICU care; indeed many needed intubation and mechanical respirator support (Wu and McGoogan 2020). Poor outcomes have also been shown to be related to the viral load; in a series of 678 hospitalized patients, Magleby et al. determined that 35% of patients with a high viral load on admission died, compared to only 18% of patients with a low viral load (Magleby et al. 2020). Some reports indicate that once mechanical ventilation is required, the mortality is very high; in a case series of 2634 patients in New York City, 373 were admitted to ICU and 320 had mechanical ventilation (81 needed renal dialysis). Nearly all of the patients requiring a ventilator died (Richardson et al. 2020).

As the severity of the illness increases, complications become more frequent. Patients in ICU may develop severe hypoxemia not readily controlled even with the help of a respirator. In some, this may reflect the development of acute respiratory distress syndrome (ARDS) which may be fatal (Driggin et al. 2020). It has also been noted that patients with COVID-19 who become increasingly ill, are more likely to develop pulmonary embolism (P. P. Liu et al. 2020); a recent study has reported that the incidence of pulmonary embolism in patients with COVID-19 and admitted to the ICU is twice that of ICU-admitted patients without COVID-19 a year earlier (Poissy et al. 2020). In general, there is a hyper-thrombotic state and in some patients, frank disseminated intravascular coagulation (DIC) develops (P. P. Liu et al. 2020; Griffin et al. 2020). A more recent publication in the New England Journal of Medicine described distinctive pulmonary vascular features, consisting of endothelial injury associated with intracellular virus and disrupted cell membranes (Ackermann et al. 2020). These features in the pulmonary vasculature were associated with widespread thrombosis, which was much more common than that observed in patients with influenza. Each of these complications significantly increases the mortality risk for patients with COVID-19.

3.4 Cardiovascular Complications

As we learn more about COVID-19, it has become more evident that cardiovascular complications are common and may account for up to 40% of deaths. It is the CV complications that appear to provide the best opportunity for an impact from our therapeutic product. Perhaps the most common CV complication in patients with COVID-19 is myocardial injury as reflected by elevation of serum troponin (P. P. Liu et al. 2020). This

might reflect myocardial cell death as a direct result of the viral infection; indeed, although uncommon, frank acute myocarditis can develop (F. Zhou et al. 2020; P. P. Liu et al. 2020),(Ruan et al. 2020), with a mononuclear cell infiltration of the myocardium at autopsy. This may be marked enough to result in the development of HF which can be severe.("ABC News, April 22, 2020," n.d.) However, a recent study from Israel suggests that the troponin release may originate more from the right ventricle than from the LV (Szekely et al. 2020). This might reflect the severity of the pulmonary infection with resultant pulmonary arterial hypertension. The development of HF in patients with COVID-19, therefore, may be multi-causal and certainly requires further study.

Other patients develop ACS with myocardial cell damage as reflected by enzyme increases and electrocardiographic abnormalities (Huang et al. 2020; P. Zhou et al. 2020). The mechanism of this is not completely clear (Tersalvi et al. 2020). In some patients, it may reflect the development of a supply-demand imbalance caused by the acute infection, hypoxemia and resulting increased heart rate (E. Y. Wang et al. 2020). But, another hypothesis is that the extreme inflammation, possibly with a cytokine storm, along with coagulation abnormalities and endothelial dysfunction, cause plaque instability in coronary arteries and results in coronary thrombosis (Tersalvi et al. 2020).

Arrhythmias are also common with atrial fibrillation being most prevalent. The pathogenesis is not clear but it is interesting that, in general, inflammation of the left atrial tissue is believed to be the common substrate for this arrhythmia. Ventricular arrhythmias also occur with resultant sudden death (P. P. Liu et al. 2020). In some cases, this has been a complication of concomitant therapy – particularly with Chloroquine or Hydroxychloroquine – both of which may prolong the QT interval. However, in a recent study from Northern Italy, investigators found that even out-of-hospital cardiac arrest was twice as common during a six-week period during the 2020 pandemic, compared to a similar period in 2019 (Baldi et al. 2020).

Finally, several recent reports highlight the high incidence of acute renal failure in patients with COVID-19 – particularly in those ill enough to require ICU management (Richardson et al. 2020). Many of these patients require replacement therapy with dialysis and have a poor prognosis. Indeed, recent Centers for Medicare and Medicaid Services (CMS) data suggest that 50% of patients hospitalized with COVID-19 had chronic kidney disease ("CMS Medicare Claims and Encounter Data" 2020).

3.5 Treatment

At the time this protocol was prepared, there were no vaccines available. More recently a number of vaccines have been approved by Regulatory Agencies in many countries. The first two approved for use in the United States were mRNA based vaccines with Phase III trial results reporting a 90-95% rate of protection from corona virus infection. Subsequently the vaccine from Astra Zeneca (which is a more standard preparation utilizing a viral vector)

has been approved and most recently a single dose vaccine by Johnson and Johnson (Janzen) has received approval.

While awaiting an effective vaccine, patients have been given supportive therapy, and when the condition deteriorates, supplemental oxygen and anti-coagulation is provided and specific treatments administered for complications. Many patients do receive corticosteroid when the lung infection becomes severe. A number of other therapies have been proposed for the viral infection and are undergoing clinical study. These include the anti-virals Umifenovir, Lopinavir/Ritonavir and Ribavirin, which have all been tried without demonstrable benefit (Driggin et al. 2020). Remdesivir is also an anti-viral developed to combat Ebola, and has offered some promise in the treatment of COVID-19 (Driggin et al. 2020). One small, uncontrolled trial suggested there might be benefit, although no definite conclusion was reached (Grein et al. 2020). In a small controlled trial in China, terminated early because of lack of patients, there was no evidence of efficacy (Y. Wang et al. 2020). However, in a recent preliminary report from an international, placebo- controlled trial, Remdesivir administered intravenously showed significant shortening of time to recovery (11 days vs 15 days in the placebo group).(“New York Times, April 30, 2020,” n.d.) Further study is required.

Other medications that have been tried and found ineffective include chloroquine and hydroxychoroquine with or without Azithromycin (P. P. Liu et al. 2020). With these medications, there was increased cardiac arrhythmia because of the propensity of these agents to prolong QT interval (P. P. Liu et al. 2020). Overall, no significant benefit has been demonstrated. The IL-6 inhibitor (Kevzara) lowered C-reactive protein but otherwise generally showed negative results (Blankenship, n.d.), whereas Tocilizumab (Actemra) in an uncontrolled study may have reduced severity of pulmonary complications (Alattar et al. 2020). Many other potential therapeutic approaches are being proposed and trialed, including blocking of the renin-angiotensin system (Patel and Verma 2020) and administration of convalescent plasma (Zeng et al. 2020). Two other of the many approaches being trialed include famotidine (the active ingredient in the over-the-counter heartburn medication Pepcid) which binds to a key enzyme in the SARS-CoV-2 virus and could make a difference (Borrell 2020). Dr. Mone Zaidi and colleagues at the Icahn School of Medicine in New York are attempting to generate a synthetic antibody which would block the SARS-CoV-2 virus from interacting with the ACE II receptor. Finally, Dr. Sara Ghandehari of Cedars-Sinai Medical Centre in Los Angeles has approval to conduct a small trial on the potential benefits of a course of therapy with progesterone in men with COVID-19. This is based on evidence that progesterone has anti-inflammatory activity and the observation that among patients with severe COVID-19, there is a preponderance of males.

3.6 Proposed Trial of Cannabidiol

Cannabidiol (CBD) is a major phyto-cannabinoid which can be extracted from hemp or the marijuana plants and is used worldwide for a large number of purported health benefits. A highly purified cannabidiol extract (Epidiolex) has recently been approved by the FDA in the

USA for the treatment of two serious childhood epilepsy syndromes (Dravet's and Lennox-Gastaut). Extensive pre-clinical data for CBD has also demonstrated significant anti-inflammatory (immunomodulatory) and cardio-protective effects. A recent publication questions whether CBD might lessen the pulmonary inflammation in COVID-19 patients (Byrareddy and Mohan 2020). Our interest is in assessing the impact of CBD on the cardiovascular complications of COVID-19 as detailed below.

Cardiol Therapeutics Inc. plans to market a pharmaceutically produced (according to current good manufacturing practice [cGMP]) CBD product (CardiolRx™) that is essentially THC-free (less than 5 ppm). Health Canada approved a CTA for a phase I study, which was completed in November of 2020. None of the 52 subjects in the study experienced a severe adverse reaction and there was no adverse impact of the drug on the QTc interval. The pharmacokinetic data were as expected from the literature. We now propose a Phase II/III study to assess the potential of CardiolRx™ to favourably modify the many cardiovascular complications of COVID-19.

3.6.1 Rationale

The hypothesis is that CardiolRx™, which is known to have anti-inflammatory and cardio-protective properties, will lessen the cardiovascular and pulmonary inflammation, preventing at least some of the significant cardiovascular complications of COVID-19, reduce the severity of effects on the lungs and reduce the length of illness overall; decreasing overall morbidity and potentially, mortality.

CBD interacts with a range of cellular receptors, which could potentially account for the anti-inflammatory activities of CBD. Published evidence indicates that CBD is active at peroxisome proliferator-activated receptor gamma (PPAR-gamma) receptors (De Filippis et al. 2011; Esposito et al. 2011; Saoirse Elizabeth O'Sullivan 2016), 5-HT1A receptors (Mishima et al. 2005; Pazos et al. 2013; Resstel et al. 2009), Adenosine A1 and A2 receptors (Alison Ribeiro et al. 2012; Carrier, Auchampach, and Hillard 2006), transient receptor potential (TRP) channels, including TRPV1, TRPV2, TRPM8, TRPA1 (Hegde, Nagarkatti, and Nagarkatti 2011; Laragione et al. 2015; Muller, Morales, and Reggio 2019), and the G-protein-coupled receptors (GPR) GPR55, GPR18, GPR6 and GPR3 (Brown 2007; Laun and Song 2017; Morales and Reggio 2017), although probably not at the canonical endocannabinoid receptors (CB) CB1 (Reggio et al. 1995; Mukhopadhyay et al. 2011; McPartland et al. 2017) and CB2.(Mukhopadhyay et al. 2011; McPartland et al. 2017)

Heart Failure: CBD improves endothelial function, and endothelial dysfunction is an important therapeutic target in a number of cardiovascular diseases including heart failure. CBD reduces inflammatory activation of the endothelial lining of blood vessels (Rajesh et al. 2007) thus improving endothelial vaso-relaxation and blood flow (Saoirse E. O'Sullivan et al. 2009; Stanley et al. 2015). As noted above, recent research results have demonstrated that the SARS-CoV-2 infects endothelial cells throughout the body resulting in an endotheliitis. Improvement in endothelial dysfunction could thereby be an important adjunctive therapy for

COVID-19. CBD has also been shown to attenuate a number of measures of potential importance in the treatment of heart failure, including cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in models of diabetes (Rajesh et al. 2010), a common co-morbidity in CVD patients. CBD has also been shown to be protective against doxorubicin-induced cardiotoxicity, including reducing pro-inflammatory responses in the heart (Fouad et al. 2013; Hao et al. 2015).

Myocarditis: A murine model of experimental autoimmune myocarditis induced by immunization with the myocarditogenic cardiac myosin peptide ($\alpha MHC_{334–352}$) resulted in T cell infiltration into the myocardium, T cell–mediated inflammation, cardiomyocyte cell death, fibrosis and myocardial dysfunction. In this model, chronic treatment with CBD (10 mg/kg, ip for 46 days) reduced the infiltration of the myocardium by inflammatory cells, decreased myocardial inflammation as reflected by lowered levels of inflammatory cytokines and chemokines (IL6, IL1-beta, interferon (IFN)-gamma, monocyte chemoattractant protein-1), reduced markers of oxidative stress and reduced myocardial fibrosis (Lee et al. 2016).

Hypertension (HTN): We investigated the effect of CBD on the cardiomyocyte cell line H9c2. H9c2 cells respond to angiotensin II by increasing in size, reflecting the myocardial hypertrophy seen in hypertension. The surface area of cultured cardiomyocytes is considerably increased by angiotensin II, and this increase is significantly decreased by CBD. Similarly, the expression of both BNP and collagen by H9c2 cells is significantly increased by angiotensin II and, again, this increase is prevented by CBD (Cardiol Therapeutics, unpublished data). In conclusion, CBD reduces the deleterious effect of angiotensin II on cardiomyocytes, including abrogating increases in cardiomyocyte size and the expression of remodeling markers.

In addition, we have used the animal model of HF in male C57BL/6 mice, based on the published method of Cordero-Reyes et al., to assess CBD effectiveness.(Cordero-Reyes et al. 2016) HF is induced by sustained hypertension (secondary to infusion of angiotensin II), which results in cardiac inflammation with associated depression of myocardial function. The results show that CBD reduced inflammation and fibrosis induced by angiotensin-II in this model. Measurements of myocyte area showed that CBD administered by sub-cutaneous injection resulted in a significant reduction at doses of both 1 and 10 mg/kg. Measurements of BNP, which is released from cardiomyocytes in response to excessive stretching and is elevated in HF, showed that CBD reduced expression of BNP in HF hearts. In conclusion, CBD administered by subcutaneous injection reduced a number of markers reflecting HF in this model system.

Arrhythmia: Data from others have also demonstrated a beneficial impact of CBD on arrhythmias resulting from experiment myocardial ischemia (Walsh et al. 2010). In this study utilizing experiment coronary artery occlusion, CBD was shown to limit the area of ischemia, whether the drug was administered before occlusion of the coronary artery or at the time of re-perfusion. In addition, quantification of ventricular rhythm abnormalities (both

ventricular premature complexes as well as runs of ventricular tachycardia) were significantly decreased in the CBD treated group.

Diabetes (DM): In an experimental mouse model of type 1 DM-induced HF, Rajesh and his colleagues demonstrated a beneficial impact of CBD on the diabetic state as well as on many of the resulting impacts on cardiac structure and function (Rajesh et al. 2010). CBD improved myocardial function, decreased inflammation and oxidative/nitrative stress, decreased expression of inflammatory cytokines and decreased fibrosis and cell death.

Pulmonary: CBD may lessen the pulmonary inflammation in COVID-19 patients.(Byrareddy and Mohan 2020) CBD decreased lung inflammation in a murine model of acute lung injury potentially.(A. Ribeiro et al. 2015) It reduced leukocyte migration into the lungs, myeloperoxidase activity in the lung tissue, protein concentration and production of pro-inflammatory cytokines and chemokines. This was associated with improved lung function, as observed by the decrease of the lung resistance and elastance.

COVID 19: In vitro studies have suggested CBD might have some direct antiviral potency,(Raj et al. 2021)

In summary, a large number of peer-reviewed studies have demonstrated that CBD has anti-inflammatory activity *in vivo* in a range of animal models of cardiovascular disease, including in a murine model of experimental autoimmune myocarditis and in *in vitro* and *in vivo* models of HF, HTN, myocardial ischemia, DM and arrhythmia. In these models, CBD has been demonstrated to be cardio-protective from insults associated with development of myocardial ischemia, arrhythmias, HTN and HF. Furthermore, there is evidence of binding of CBD to a range of different receptors, a number of which are associated with anti-inflammatory activities. This adds to the rationale for the administration of CBD as a therapeutic approach in the treatment of COVID-19 to lessen the pulmonary inflammation, hopefully reducing the overall severity and length of illness as well as help prevent the development of cardiovascular complications which add significantly to the morbidity and mortality from the disease.

4 STUDY OBJECTIVES

4.1 Efficacy

4.1.1 Primary Objective

The primary objective of this study is to evaluate the effect of CardiolRx™ on prevention of cardiovascular and COVID-19 complications in patients hospitalized for COVID-19.

4.1.2 Primary Efficacy Outcome

The primary composite endpoint in this study is to experience one of the following events during the first 28 days post randomization:

- All-cause mortality
- Requirement for ICU admission and/or ventilatory support due to COVID-19
- CV complications*:
  - HF or
  - AMI or
  - myocarditis
  - new sustained or symptomatic arrhythmia or
  - stroke

*see Appendix 17.8 for definitions

4.1.3 Secondary Efficacy Objectives

Secondary objectives include the improvement in other clinical parameters during 28 days post randomization.

4.1.4 Secondary Efficacy Parameters

The secondary efficacy parameters include the following:

- …Win Ratio of Ordinal Outcome Scale endpoint:
  1) not hospitalized and no limitations of activities;
  2) not hospitalized, with limitation of activities, home oxygen requirement, or both;
  3) hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care
  4) hospitalized, not requiring supplemental oxygen but requiring ongoing medical care
  5) hospitalized, requiring any supplemental oxygen;
  6) hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices;
  7) hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
  8) MI or stroke diagnosed since randomization
  9) death.

- Change in hs-troponin from baseline to peak elevation during the 28-day treatment period
- Change in TNF-alpha from baseline to peak elevation during the 28-day treatment period

4.1.5 Other Efficacy Parameters

Other efficacy parameters include the following:

- Percentage of patients developing any one of the primary endpoint components within 60 days post randomization
- CV mortality at 28 days post randomization
- Percentage of patients requiring dialysis within 28 days post randomization
- Win ratio of the Ordinal Outcome Scale endpoint within 60 days of randomization
- PICQ at Day 28 and at Day 60
- Development of severe lymphopenia, defined as < 1000 cells/ microliter within 28 days post randomization
- Change in (elevation of) hs-troponin, NT-proBNP, D-dimer and in inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10) from baseline to Day 7 (AUC)
- Change from baseline to peak elevation of NT-proBNP, D-dimer and in inflammatory markers (hs-CRP, ferritin, IL-1 beta, IL-6, IL-10) during the 28-day treatment period
- Change from baseline to peak elevation of LDH during the 28-day treatment period
- Difference in CMR parameters: LVEF, LVEDV, LVESV, LAESV, ECV, GLS, LV mass, LGE extent and edema between the two treatment groups after 4 weeks of study treatment (in a subset of patients at selected sites).

4.2 Safety

4.2.1 Safety Objective

The primary safety objective is to demonstrate that administration of CardiolRx™ in the proposed doses in this patient population is safe.

4.2.2 Primary Safety Endpoints

The primary safety endpoint is the number of SAEs and AEs during the 60-day study period.

4.2.3 Secondary Safety Endpoints

The secondary safety endpoints include changes in C-SSRS, blood chemistry and hematology parameters (including lymphocyte count), ALT, AST, bilirubin, eGFR, creatinine, INR and QTc interval from ECG recordings 5 hours post morning dose (time window 3.5 – 6 hours) during 28 days of study drug administration.

4.3 Study Drug Levels

CBD levels will be measured at baseline, at Days 3, 5, 7, and 28.

5 STUDY POPULATION

5.1 Enrolment and Study Centers

422 patients will be randomized (211 to CardiolRx™ and 211 to placebo) in this multi-centre trial.

5.2 Inclusion Criteria

The following inclusion criteria must be met to enroll a patient into this study:

1. Males and females 18 years of age or older
2. Hospitalized for COVID-19 with the most recent test positive*; not receiving or likely to receive invasive mechanical ventilation within the next 24 hours
3. Prior history of at least one of:
   - i) CVD [cardiovascular (CV), cerebrovascular or peripheral vascular diagnoses],
   - ii) Age > 64,
   - iii) Diabetes (DM),
   - iv) Hypertension (HTN),
   - v) Abnormal serum lipids,
   - vi) Obesity (BMI≥30 or waist circumference >102 cm [40”] for men and >88 cm [35”] for women),
   - vii) Current smoker

   * Must be PCR test.

5.3 Exclusion Criteria

None of the following criteria can be present if a patient is to be enrolled in this study:

1. Patients who have received vasopressors, extracorporeal membrane oxygenation and mechanical ventilation within last 30 days
2. Background of cardiac transplant surgery
3. Implanted defibrillator (ICD) in the last month
4. Implanted left-ventricular assist device (LVAD)
5. Acute coronary syndrome (ACS) within 30 days
6. Percutaneous coronary intervention (PCI) within 30 days
7. Receiving immuno-suppressive therapy other than dexamethasone
8. History of QT interval prolongation
9. Treated with strong inducers CYP3A4 or CYP2C19, as listed in Appendix 17.7
10. QTc interval > 500 msec (please refer to section 9.2.3 for BBB correction)
11. Chronic renal failure, as defined as eGFR < 30 ml/min

12. Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 times the upper limit of normal (ULN) **or** Alt or AST >3x ULN plus bilirubin >2x ULN
13. Bacterial sepsis, defined as documented bacteremia at the time of presentation or other active bacterial infection
14. Current participation in any research study involving investigational drugs or devices with the exception of dexamethasone, remdesivir, baricitinib plus remdesivir, convalescent plasma or monoclonal antibodies against the SARS-CoV-2 virus or any other therapy approved under emergency use in the region for treatment of COVID-19
15. Inability or unwillingness to give informed consent
16. Ongoing drug, alcohol or cannabis abuse (in the opinion of the investigator)
17. Women who are pregnant or breastfeeding
18. Any factor, which would make it unlikely that the patient can comply with the study procedures
19. Hemoglobin < 8.5 gm/dL
20. Leukocyte count < 3000/ mm^3
21. Platelets < 100,000 / mm^3
22. Current diagnosis of cancer, with the exception of non-melanoma skin cancer
23. Showing suicidal tendency as per the C-SSRS, administered at screening
24. Any cannabinoid intake in the past month
25. Body weight > 170 kg

6 STUDY DESIGN

6.1 Summary of Study Design

Multi-center, double-blind, randomized, placebo-controlled, parallel group design. 1:1 randomization.

Screening (Assessment Day 0-1): Patients hospitalized for COVID-19 will be screened. If patient consent can be obtained, baseline assessments will be carried out: Physical examination (including vital signs), ECG (including QTc interval assessment), echocardiography, chest X-ray, local laboratory assessments, including CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR, serum pregnancy test (in women with child-bearing potential only), glucose, total cholesterol, lymphocyte count and LDH. Frozen samples will be retained for central analysis of CardiolRx™ levels, hs-troponin, NT-proBNP, D-dimer as well as inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta IL-6, IL-10). A C-SSRS will also be completed.

If all eligibility criteria are met, the patient will be randomized to either CardiolRx™ or placebo.

Study treatment will be initiated in the evening of Day 1, after all baseline assessments have been completed and the patient is randomized. Study medication must be taken with food. The maximum dosing period of patients will be 28 days.

Oral administration is as follows:

Study Day	**a.m. dose [mg/kg of body weight]** CardiolRx™ or placebo	**p.m. dose [mg/kg of body weight]** CardiolRx™ or placebo
1	N/A	2.5
2	2.5	2.5
3	2.5	5
4	5	5
5	5	7.5
6 - 28	7.5	7.5

If the next higher dose is not tolerated, the dose will be reduced to the previous tolerated dose. The highest tolerated dose will be administered until Day 28.

At each study visit, drug accountability will be done. New bottles of study medication will be dispensed at each study visit (Days 3, 5, 7, 14 and 21).

6.2 Initial procedures

On Days 3, 5, and 7 vital signs and an ECG will be recorded at 5 hours post morning dose (time window 3.5 – 6 hours) with QTc interval assessed. If the QTc interval is > 500 msec or shows an increase of > 60 msec from baseline, the study medication must be stopped immediately.
In addition to prolongation of the QTc, careful observation is required to detect other ADRs and DDIs. Because CardiolRx™, inhibits a number of CYP and uridine diphosphate glucuronosyl transferase (UGT) enzymes, the metabolism of other drugs may be impaired, thereby resulting in increased concomitant drug blood levels; therefore, new symptoms may represent toxicity from a concomitant medication that had previously been well tolerated. For more detailed discussion, see section 6.3 of the IB.

In addition, to aid investigators in screening concomitant medications for risk of DDIs, a table of medications that serve as substrate for certain enzyme isoforms inhibited by CardiolRx™ has been prepared (Appendix 17.10).

Frozen samples will be retained for central analysis of CBD levels, hs-troponin, NT-proBNP, D-dimer as well as inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10) and additional parameters of interest every two days until Day 7 as well as on Day 28.

If the patient is discharged before Day 7, the assessments up to Day 7 will be carried out as out-patient or home visits.

After Day 7, all remaining scheduled assessments will be carried out during out-patient visits.

6.3 Follow-up procedures

After Day 7, routine assessments will be carried out on a weekly basis until Day 28.

On Day 28 the assessments include the following: Physical examination (including vital signs), ECG (recorded 5 hours post morning dose [time window 3.5 – 6 hours] for assessment of QTc interval), echocardiogram to measure LVEF, chest X-ray and local and central laboratory assessments, including CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR, lymphocyte count and LDH. In addition, a C-SSRS will be completed and the patient will be asked to answer a PICQ. A subset of patients at selected sites will also undergo a CMR assessment, either on Day 28 or 45.

Further follow-up visits are scheduled for Day 45 and Day 60 post randomization. These include a clinical assessment, including vital signs as well as the completion of the PICQ (at Day 60 only).

Changes in concomitant medications, AEs and SAEs will be recorded during all study visits after consent has been obtained.

6.4 Randomization Procedure

Randomization will be accomplished by means of a web-based randomization system and will be stratified by center.

The randomization sequence will be generated by random computerized sequence in blocks of 4.

6.5 Study Medication

6.5.1 Active Study Medication

CardiolRx™ (cannabidiol) oil contains cannabidiol at a concentration of 100 mg/ml. Inactive ingredients include medium-chain triglyceride (MCT) oil and Vitamin E:

Component	Function	Strength	
		10% w/v	
		Quantity per ml	%
-(-) Cannabidiol	Active pharmaceutical ingredient (API)	100 mg/ml	10% w/v
Vitamin E	Anti-oxidant	10 mg/ml	1.0% w/v
Medium Chain Triglycerides	Solvent	0.890 ml	89.0% w/v
Total		1 ml	100.0%

6.5.2 Placebo

The placebo contains all of the inactive ingredients and none of the active ones:

Component	Function	Strength (label claim)	
		Placebo	
		Quantity per mL	%
Vitamin E	Anti-oxidant	10 mg/ml	1.0 % w/v
Medium Chain Triglycerides	Solvent	q.s. to 1 ml	~99%
Total		1 ml	100%

6.6 Blinding

Placebo will match active study drug in odor, taste, color and appearance to assure proper blinding.

6.7 Premature Interruption or Withdrawal from Study Treatment

Prior to suspending the study treatment, permanently or temporarily, if possible, the investigator needs to contact the Medical Monitor to discuss the reason(s) for suspension.

6.7.1 Permanent Suspension of Study Treatment

The investigator may permanently suspend the treatment in the following cases:

- If the patient's QTc interval is > 500 msec or an increase from baseline of > 60 msec is observed (please refer to section 9.2.3 for BBB correction);
- A DDI is identified with a concomitant medication that is medically required and cannot be resolved without the discontinuation of the study medication;

- If, in the view of the investigator, the patient experiences a severe allergic reaction that cannot be explained by the administration of any other medication;
- Development of liver function abnormality, as described in section 9.2.14.3.
- Development of an AE or any medical condition, which, in the opinion of the investigator, necessitates permanent suspension of study treatment;
- Withdrawal of consent.
- If the blind is broken (only allowed in emergency situations to determine appropriate patient care)

Patients have the right to discontinue study treatment for any reason. However, unless they withdraw consent and are no longer willing to participate, they should be followed for the remainder of the trial and all (S)AEs should be reported, regardless of whether or not the event is of CV origin or occurs under the care of another physician or institution.

6.7.2 Temporary Suspension of Treatment

Temporary suspension of study treatment (up to 5 days) can occur in case of development of an (S)AE or a medical condition, which, in the opinion of the investigator, necessitates temporary interruption of study treatment, including a new finding of eGFR < 30 ml/min.

After temporary interruption of study treatment, all efforts should be made to re-institute study treatment using the last tolerated dose as soon as the clinical condition of the patient has stabilized.

6.7.3 Withdrawal of Consent

Patients may decide to fully or partially withdraw their consent to participate in the study. At that point, it should be established, whether the withdrawal is related to study treatment, further assessments, or any further involvement in the study. If the withdrawal is primarily related to study treatment or specific assessments, patients should be encouraged to continue follow-up and to attend all other subsequent study assessments. Reports of AEs and SAEs should be collected until completion of the study for all withdrawals, unless the patient objects to such follow-up.

Patients who withdraw their consent to participate in the study, whether related to study treatment or not, will not be replaced. All data available will be included in the statistical analysis.

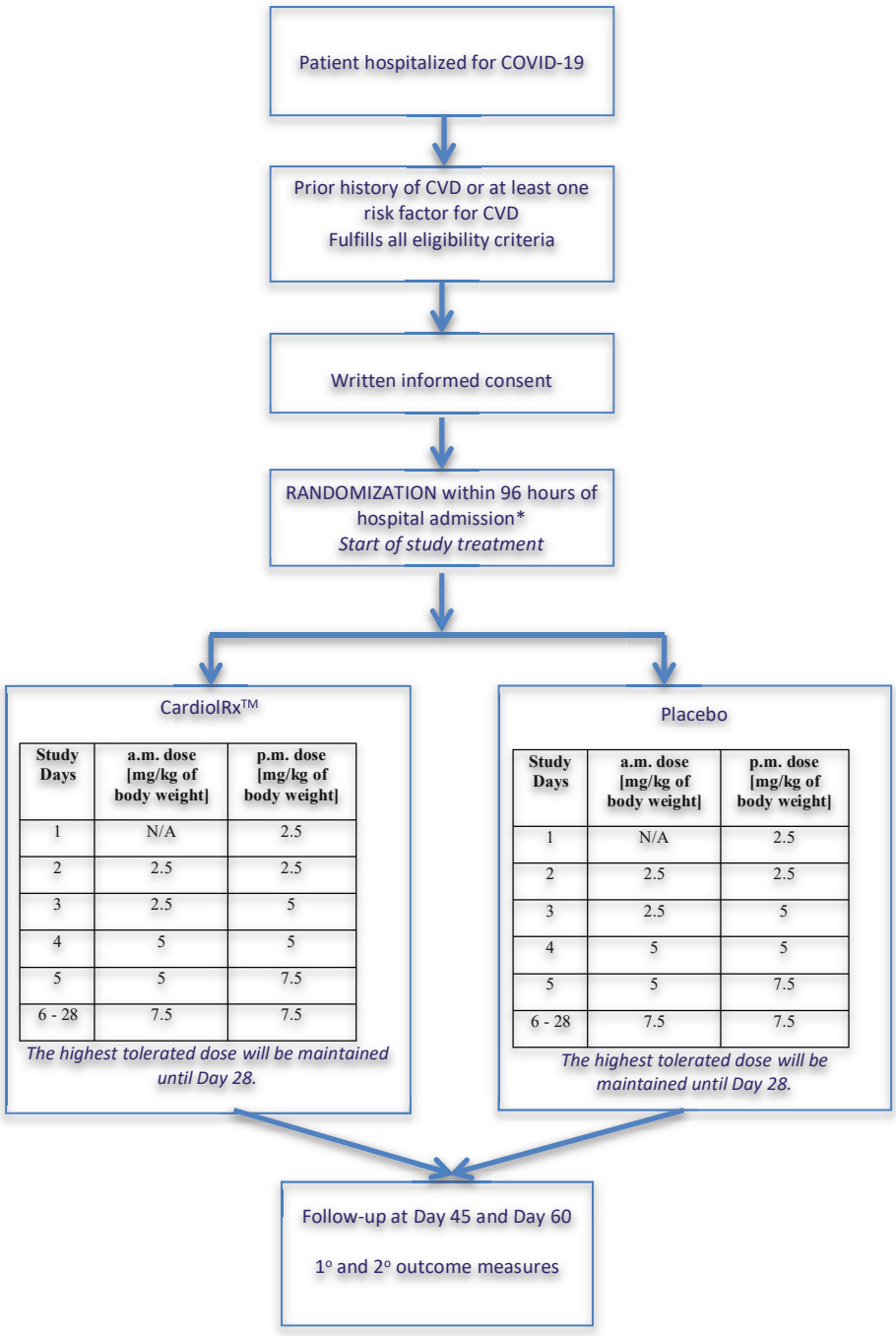
6.8 Concomitant Treatment

Patients may be on SOC treatment(s) for all current conditions, as prescribed by their treating physician, including dexamethasone, remdesivir, baricitinib plus remdesivir, monoclonal antibodies (administered prior to admission), and convalescent plasma therapy,

with the exception of cannabinoids and strong inducers of CYP3A4 and CYP2C19 (see Appendix 17.7).

Also, because CardiolRx™ is known to inhibit the metabolism of certain other drugs, new symptoms or findings may represent toxicity from a concomitant medication that had previously been well tolerated. Please refer to section 9.2.11 and to Appendix 17.10.

7 STUDY PLAN



* Patients awaiting planned admission to hospital in an emergency room for less than 96 hours can be screened and enrolled into the trial.

8 INVESTIGATIONAL PRODUCTS, DOSE AND DURATION OF TREATMENT

8.1 Investigational Product

CardiolRx™ is pharmaceutically produced. It contains cannabidiol in a concentration of 100 mg/ml and is free of tetrahydrocannabinol (THC; <5 ppm).

8.2 Administration, Dosage and Duration of Treatment

Study drug will be administered orally (via syringe)* with food according to the following treatment schedule:

Study Day	a.m. dose [mg/kg of body weight] CardiolRx™ or placebo	p.m. dose [mg/kg of body weight] CardiolRx™ or placebo
1	N/A	2.5
2	2.5	2.5
3	2.5	5
4	5	5
5	5	7.5
6 - 28	7.5	7.5

At each study visit, drug accountability will be done. New bottles of study medication will be dispensed at each study visit (Days 3, 5, 7, 14 and 21).

If the next higher dose is not tolerated, the patient should return to the last tolerated dose. The highest tolerated dose will be administered until Day 28 (4 weeks post randomization).

The maximum treatment period will be 28 days.

* If the patient requires mechanical ventilation, the study medication is administered through a naso-gastric tube.

Justification for Dosing Regimen

COVID-19 is an acute illness with, at times, rapid progression of symptoms and signs. Because of this, it seems important to increase the blood level of the investigational agent as quickly as possible to achieve the potential anti-inflammatory and anti-cytokine actions that are likely to be important in this population. However, this agent has not been administered previously to this population, so care must be taken to observe closely for

adverse drug effects or drug-drug interactions that might have significant negative consequences. A similar product containing a highly purified botanical extract of CBD has been approved for use in pediatric epilepsy to a dose up to 10 mg/kg twice daily (Devinsky et al. 2016). We have chosen to restrict the maximum dose in this COVID-19 population to 7.5 mg/kg b.i.d. because of the expected elderly and perhaps frail condition of some of the enrolled patients. Investigators are encouraged to decrease the dose if there are indications of intolerance of a given dose to the previously tolerated dose.

8.3 Study Treatment Return and Reconciliation

A detailed treatment dispensing log will be kept at each site, which will be checked at the close-out visit. After completion of the study, including final drug accountability, all unused study materials must be destroyed locally.

8.4 Supply, Packaging, Labelling and Storage

8.4.1 Supply and Packaging

The study drug will be provided in 30 ml bottles, containing a concentration of 100 mg/ml.

8.4.2 Labelling and Storage

All study medication will be labeled in both English and the local language according to the local regulations for investigational drugs.

All clinical drug supplies are to be stored in a secure, limited-access area in accordance with labeled storage conditions:

- Controlled temperature 20°C - 25°C (68°F- 77°F) or refrigerated. Excursions up to 30° C (86 °F) that are experienced in pharmacies, hospitals, and warehouses, and during shipping are allowed, provided they do not exceed 24 hours.
- The relative humidity should not exceed 65%
- The study supplies need to be protected from light (to be kept in closed cartons or boxes).

If the patient is discharged before Day 28, the patient will administer the study medication at home. If the temperature range of < 25°C cannot be achieved in the patient's home, the patient will be asked to store the study medication in the fridge.

9 CONDUCT OF THE STUDY

9.1 Scheduling of Study Procedures

Patients hospitalized for COVID-19 with a prior history of CVD or at least one risk factor for CVD will be screened.

Day 0-1 -- Baseline assessments and Randomization and start of study medication
The following evaluations will be performed a baseline:

- Written informed consent
- Clinical assessment
- Demographics
- Medical History/Current conditions, including prior CV events and interventions
- Concurrent medication and CV medication history for the previous 24 weeks
- C-SSRS
- Vital signs, including heart rate (HR), blood pressure, height and weight
- Chest X-ray
- 12-lead ECG, including QTc interval assessment
- LVEF by echocardiography
- Assessment of Ordinal Outcome Scale
- Local laboratory assessments, including CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR, serum pregnancy test (in women with child-bearing potential only), glucose, total cholesterol, lymphocyte count and LDH
- Retention of frozen samples for hs-troponin, NT-proBNP, D-dimer, hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10 and additional parameters of interest
- Retention of frozen samples for CBD levels

Randomization and start of study medication (2.5 mg/kg b.i.d.) in the evening of Day 1 after all baseline assessments have been completed and all eligibility criteria are met. Randomization must be no later than 96 hours after hospital admission. Patients awaiting planned admission to hospital in an emergency room for less than 96 hours can be screened and enrolled into the trial.

Day 3

- Vital signs, including HR and blood pressure
- 12-lead ECG, including QTc interval assessment 5 hours post morning dose (time window 3.5 – 6 hours)
- Assessment of Ordinal Outcome Scale
- AE and SAE recording
- Recording of changes in concomitant medications
- Study drug dose increase to 5.0 mg/kg b.i.d., if previous dose is well-tolerated
- Study drug accountability
- Retention of frozen samples for hs-troponin, NT-proBNP, D-dimer, hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10 and additional parameters of interest

- Retention of frozen samples for CBD levels

Day 5
- Vital signs, including HR and blood pressure
- 12-lead ECG, including QTc interval assessment 5 hours post morning dose (time window 3.5 – 6 hours)
- Assessment of Ordinal Outcome Scale
- AE and SAE recording
- Recording of changes in concomitant medications
- Study drug dose adjustment to 7.5 mg/kg b.i.d., if 5.0 mg/kg b.i.d. is well-tolerated (If 5.0 mg/kg b.i.d. is not tolerated, then dose decrease back to 2.5 mg/kg b.i.d.)
- Study drug accountability
- Retention of frozen samples for hs-troponin, NT-proBNP, d-dimer, hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10 and additional parameters of interest
- Retention of frozen samples for CBD levels

Day 7
- Clinical assessment
- Vital signs, including HR, blood pressure and weight
- 12-lead ECG, including QTc interval assessment 5 hours post morning dose (time window 3.5 – 6 hours)
- Assessment of Ordinal Outcome Scale
- AE and SAE recording
- Recording of changes in concomitant medications
- Study drug dose adjustment and accountability
- Local laboratory assessments, including CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR, lymphocyte count and LDH
- Retention of frozen samples for hs-troponin, NT-proBNP, D-dimer, hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10 and additional parameters of interest
- Retention of frozen samples for CBD levels

If the patient is discharged before Day 7, the assessments up to Day 7 will be carried out as out-patient or home visits. After Day 7, all remaining scheduled assessments will be carried out during out-patient visits.

Time windows for out-patient visits or home visits up to Day 7 are +/- 1 day; after Day 7, time windows are +/- 2 days.

Day 14
- Clinical assessment
- Vital signs, including HR, blood pressure and weight
- 12-lead ECG, including QTc interval assessment 5 hours post morning dose (time window 3.5 – 6 hours)
- Assessment of Ordinal Outcome Scale

- AE and SAE recording
- Recording of changes in concomitant medications
- Study drug dose adjustment and accountability
- Local laboratory assessments, including CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR, lymphocyte count and LDH

Day 21
- Clinical assessment
- Vital signs, including HR, blood pressure and weight
- 12-lead ECG, including QTc interval assessment 5 hours post morning dose (time window 3.5 – 6 hours)
- Assessment of Ordinal Outcome Scale
- AE and SAE recording
- Recording of changes in concomitant medications
- Study drug dose adjustment and accountability

Day 28
- Clinical assessment
- Vital signs, including HR, blood pressure and weight
- Chest X-ray
- 12-lead ECG, including QTc interval assessment 5 hours post morning dose (time window 3.5 – 6 hours)
- LVEF by echocardiography
- Assessment of Ordinal Outcome Scale
- CMR (subset of patients at selected sites)
- C-SSRS
- PICQ
- AE and SAE recording
- Recording of changes in concomitant medications
- Study drug accountability
- Local laboratory assessments, including CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR, lymphocyte count and LDH
- Retention of frozen samples for hs-troponin, NT-proBNP, D-dimer, hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10 and additional parameters of interest
- Retention of frozen samples for CBD levels

Day 45
- Clinical assessment
- Vital signs, including HR, blood pressure and weight
- Assessment of Ordinal Outcome Scale
- Recording of changes in concomitant medications
- AE and SAE recording
- CMR if not recorded on Day 28 (subset of patients at selected sites)

Day 60
- Clinical assessment
- Vital signs, including HR, blood pressure and weight
- PICQ
- Assessment of Ordinal Outcome Scale
- Recording of changes in concomitant medications
- AE and SAE recording

9.2 Clinical Procedures and Safety Evaluations

9.2.1 Informed Consent

Patients hospitalized for COVID-19 with a prior history of CVD and/or at least one risk factor for CVD will be approached and informed of the possibility of study participation. The benefits and risks of participating in the study will be explained to the patient. The patient will be provided with an opportunity to read the detailed information about the study in an informed consent form (ICF) and ask any questions he/she may have. Prior to conducting any study-related procedures, the patient must provide consent to participate by signing the Institutional Review Board/Research Ethics Board (IRB/REB) approved ICF.

9.2.2 Demography

This includes age, sex and race.

9.2.3 Standard 12-lead Electrocardiogram (ECG)

A 12-lead ECG will be performed at baseline, at Days 3, 5, 7, 14, 21, and 28 5 hours post morning dose (time window 3.5 – 6 hours).

The effect of CBD (CardiolRx™) on cardiomyocyte ion channel function has not been reported to date. One study assessed the effect of a product with equal THC and CBD content (Sativex) on QTc (Sellers et al. 2013). No effect was found. In the Abstracts of the 2017 meeting of the American Epilepsy Society, Van Landingham et al. from GW Pharmaceuticals presented the PK data for single normal and large doses of their CBD and assessed the impact on QTc (VanLandingham et al. 2017). No impact was identified. Another study of the effects of CBD on QT interval in children and young adults with epilepsy syndromes is listed on Clinical Trials.gov but was not completed because the investigator has been on medical leave and recruitment was difficult. Cardiol has contracted to have half-maximal inhibitory concentration (IC 50) values recorded for sodium, potassium and calcium channels in a human cardiac cell line. Until those results are available, the FDA has requested that the QTc intervals on repeated ECG recordings at the times of peak blood levels of CBD and its major metabolites are assessed after the morning dose of study medication. The time to peak blood level for CBD and its two major metabolites (7-hydroxy CBD and 7-Carboxy CBD) has been reported to be at approximately 4 hours after the dose has been taken (Tayo et al. 2020; Taylor et al. 2018). In our Phase I study the maximum concentration occurred at 5 hours post dose; this interval is specified for this protocol.

As noted in section 6.3 of the IB, there is considerable potential for drug-drug interactions (DDIs) in the patient population under study. Of particular concern is the potential for CBD to inhibit the metabolism of a drug(s) that has the ability to prolong the QTc interval. Therefore, if the QTc does increase after the institution of the study drug, the Investigator should consider this possibility, identify the concomitant medication responsible for it and adjust the dose of the medication as appropriate.

Because of this concern, an electrocardiogram (ECG) will be recorded every other day for the first 7 days of drug dosing and on Days 14, 21 and 28; the recording should be done 5 hours after the morning dose of the study drug (time window 3.5 – 6 hours). The ECG will be assessed by the Investigator at the clinical site, the QT interval measured (the QTc calculated) and recorded in the case report form (CRF), with a copy of the ECG appended. The QT interval is measured from the beginning of the QRS complex to the end of the T wave and averaged over three cardiac cycles. The average QT interval should be corrected for heart rate variability using Bazett's formula ($QT_c = QT / \sqrt{RR}$) or Fridericia's formula ($QT_c = QT / RR^{1/3}$) to create the QTc interval. Each patient should have the QTc measured using the same method on all designated days in the study. If the QTc interval increases to 500 msec or more – or increases 60 msec or more from the baseline recording on any one measurement, this will be reported as an SAE and the study medication will be discontinued.

The QT interval can be obtained from the automated measurements of the ECG recorder, unless the data quality is poor. It is the corrected value that is to be recorded in the CRF.

After 100 patients have completed the Day 28 assessment (or terminated the study earlier), the QTc data will be analyzed (unblinded) by the DSMC. If an impact on the QTc interval by the study drug has been found, the DSMC will evaluate the appropriateness of continuing the trial.

The presence of a bundle branch block represents a particular challenge in properly measuring the QTc interval. Following international recommendations, QT interval should be measured in leads showing the longest QT interval, which is usually in right precordial leads. In presence of a BBB, these leads are strongest affected by conduction delay and therefore hamper adequate measurement. A new formula for evaluation of the QT interval in patients with left bundle branch block (LBBB) was introduced in 2014:

$QT_{mean} = QT_{BBB} – 50\% \, QRS_{BBB}$(Bogossian et al. 2014)

This formula has proved to be a reliable tool in clinical practice for QTc interval evaluation in patients with LBBB, right bundle branch block (RBBB) or bifascicular block. (Bogossian et al. 2020; Erkapic et al. 2020)

If the QTc interval increases to 500 msec or more – or increases 60 msec or more from the baseline recording on any one measurement, this must be reported as an SAE and the study medication must be discontinued.

Other clinically relevant ECG changes also need to be reported as an AE or SAE.

9.2.4 LVEF assessment by Echocardiography

The patient's LVEF will be assessed at baseline and at Day 28.

Each study will include 2-D echo images obtained from the standard parasternal and apical windows, with care taken to ensure on-axis views from all acoustic windows. LVEF will be calculated by standard techniques. LV cavity dimensions in systole and diastole will be measured, as well as thickness of the interventricular septum and posterior wall according to current guidelines. LV mass and mass index normalized for body surface area will be calculated using standard formulae (Otterstad et al. 1997).

Biplane Simpson's method (Devereux et al. 1986) will be used for measurement of LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes. Volume measurements obtained by this method have been shown to be both accurate and reproducible, with variation in the range of -5% to +5%. It is anticipated that the image quality will be adequate for accurate endocardial tracing in > 90% of patients.

LVEDV, LVESV, and LVEF will be calculated and averaged over 5 cardiac cycles, 10 cardiac cycles in patients with atrial fibrillation.

9.2.5 Medical History

Data will be collected from patients at baseline consisting of medical history, including previous cardiac investigations, previous cardiac history, and current medications.

9.2.6 Clinical assessment

A routine clinical assessment is required at baseline, at Days 7, 14, 21, 28, 45 and 60. Any abnormality must be recorded.
Any subsequent change and new finding must be documented at each scheduled clinic visit, and reported as an (S)AE, if applicable.

9.2.7 Vital signs, body height and weight

Vital signs including blood pressure and heart rate will be recorded at each clinic assessment/visit. A calibrated sphygmomanometer and a cuff size appropriate for the patient's arm circumference will be used. The patient must be sitting, and must have rested for at least 5 minutes. The diastolic blood pressure is to be read at the disappearance of sounds (Korotkoff phase 5). If the disappearance of sound is not detectable, phase IV should be used. Any clinically relevant change in blood pressure or HR must be reported as an AE or SAE.

Body height is to be measured at baseline. Body weight must be measured at baseline, at days 7, 14, 21, 28, 45 and 60. Body weight at baseline will be used for the calculation of the amount of study medication to be administered throughout the treatment period.

9.2.8 Ordinal Outcome Scale

The scores for the Ordinal Outcome Scale will be collected at each visit:

1) not hospitalized and no limitations of activities;
2) not hospitalized, with limitation of activities, home oxygen requirement, or both;
3) hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care
4) hospitalized, not requiring supplemental oxygen but requiring ongoing medical care
5) hospitalized, requiring any supplemental oxygen;
6) hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices;
7) hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
8) MI or stroke diagnosed since randomization
9) death.

9.2.9 Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire designed for the assessment of suicidal ideation and behavior in adolescents and adults.

To monitor for the emergence of suicidal ideation and behavior, subjects will undergo C-SSRS evaluations at baseline and at Day 28.

The questionnaire must be administered by an investigator or other individual that is suitably qualified by education or training. See Appendix 17.4 for a sample C-SSRS – Baseline/Screening version assessment and Appendix 17.5 for a sample 28-day post-dose C-SSRS assessment.

If there is a positive result for suicidality on the C-SSRS after screening (defined by a subject answering ‘yes’ to questions 4 or 5 on the suicidal ideation portion of the C-SSRS), the subject will be evaluated by an investigator or medically qualified sub-investigator for continuation in the study.

If a subject becomes suicidal during the study, an investigator or medically qualified sub-investigator should provide the appropriate treatment to the subject.

9.2.10 Patient Impression of Change Questionnaire (PICQ)

On Day 28 and on Day 60, the patient will be asked to complete a PICQ. It collects the patient’s impression on how his/her overall status has changed from baseline. A copy can be found in section 17.3 of this protocol.

9.2.11 Concomitant treatment

Medications will not be altered for the purpose of this trial, however, any medication changes during screening must be recorded, as must those started before randomization and continued thereafter. At each study assessment, changes in concomitant treatment must be recorded. To allow for accurate information about all medication a patient was

taking at the moment an (S)AE occurred, stop and start dates of concomitant medications must be recorded throughout the study.

Because CardiolRx™ is known to inhibit the metabolism of certain other drugs, new symptoms or findings may represent toxicity from a concomitant medication that had previously been well tolerated. For more detailed discussion of DDIs, see the IB, Section 6.3.

In addition, to aid investigators in screening concomitant medications for risk of DDIs, a table of medications that serve as substrate for certain enzyme isoforms inhibited by CardiolRx™ has been prepared (Appendix 17.10).

9.2.12 Laboratory tests

9.2.12.1 Local laboratory tests

Local laboratory tests include CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR, glucose, total cholesterol, lymphocyte count and LDH as well as a serum pregnancy test (beta-hCG, female patients of child bearing potential and at baseline only).

Please see Appendix 17.2.2 for the exact schedule of all laboratory tests.

9.2.12.2 Additional laboratory tests

In addition to local laboratory tests, frozen samples will be retained for the following tests to be analyzed by a central laboratory: hs-troponin, NT-proBNP, D-dimer, hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, as well as CBD levels and additional parameters of interest. **These will not be used for genetic testing.**

Please see Appendix 17.2.2 for the exact schedule of all laboratory tests.
All samples will be stored at -70°C at the sites and will be shipped to the Central Laboratory in batches.

9.2.13 Cardiac magnetic resonance imaging (CMR)

A subset of patients at selected sites will undergo a CMR at Day 28. The standardized examination protocol (Appendix 17.11) will include LVEF, LVEDV, LVESV, LAESV, ECV, GLS, LV mass, LGE extent and edema. All images will be analyzed at a Central CMR Core Laboratory.

9.2.14 Management of AEs

9.2.14.1 AE Reporting

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this

treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. (In order to prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs.)

Any AE that results in any of the following outcomes will be considered an SAE:

1. Death
2. Life-threatening situation (Patient was at risk of death at the time of the event. This does not refer to an event that might have caused death if it was of greater intensity.)
3. New in-patient hospitalization or prolongation of existing index hospitalization
4. Persistent or significant disability or incapacity
5. Congenital anomaly or birth defect
6. Important medical events that may not result in death, be life-threatening, or require hospitalization but may jeopardize the patient and may require medical or surgical intervention to prevent one of the above outcomes (based upon appropriate medical judgment), e.g., allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse. Potential DILI is also considered an important medical event. (See Section 9.2.14.3 for the definition of potential DILI.)

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe pain); the event itself, however, may be of relatively minor medical significance (such as severe headache). By contrast, the term “serious” is used to describe an event based on an event outcome or actions usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

For all collected SAEs, the clinician who examines and evaluates the patient will determine the event’s causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

Possibly Related: There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event.

Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable and in which other drugs or chemicals or underlying disease provides plausible explanations.

Not related: The S*AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology.*
Pre-existing conditions should be recorded upon patient enrolment (including start date of the condition, and severity - mild, moderate, severe). After the patient signs the informed consent form, any worsening of these conditions would be recorded.
Any new conditions would be recorded including date of onset, date of resolution, severity (mild, moderate, severe, or serious as defined above) and possible relationship to study drug or procedure. As part of the source notes, follow up clinical assessments, laboratory tests, ECGs and diagnostic imaging related to the AE should be documented.

All (S)AEs will be followed until resolved or until a stable condition is reached (as assessed by the Investigator). Follow-up information on patients discontinued from the study due to an SAE must be collected for a minimum period of one (1) month.

9.2.14.2 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study patient is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives (18 days) after product administration, the investigational product will be permanently discontinued and the pregnancy will be reported to the Sponsor and the Contract Research Organization (CRO) within 24 hours of the site's awareness of the event. Worldwide Clinical Trials (WWCT) has been contracted as the CRO for this trial. Protocol-required procedures for study discontinuation and follow-up must be performed on the patient unless contraindicated by pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated.

9.2.14.3 Drug-Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria below, must be reported as SAEs.

Potential DILI is defined as:

1. ALT or AST elevation > 8 x ULN

OR

2. ALT or AST elevation > 5 x ULN for more than 2 weeks

OR

3. ALT or AST elevation > 3 x ULN and bilirubin >2 x ULN or INR > 1.5.

If a patient meets one of the above criteria, the study drug needs to be discontinued and the assessments of ALT, AST, bilirubin and alkaline phosphatase, as well as a physical examination need to be repeated every 24 hours until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state.

Elevations in ALT or AST > 3 × ULN or bilirubin > 2 × ULN alone, i.e., when not concomitant, are not grounds for withdrawal but are to be followed up, as above, within 72 hours of notice of abnormal results.

9.2.14.4 Overdose

All occurrences of overdose must be reported as SAEs. An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

9.2.14.5 Drug-Drug Interactions

CardiolRx™ is known to be metabolized largely through the cytochrome P450 enzyme system in the liver. A number of the drugs commonly used in the management of cardiovascular or concomitant conditions are also capable of being inducers or inhibitors of these enzymes. The patients should specifically be monitored for (S)AEs that might reflect DDIs. See section 6.3 of the IB for more detailed discussion.

In addition, to aid investigators in screening concomitant medications for risk of DDIs, a table of medications that serve as substrate for certain enzyme isoforms inhibited by CardiolRx™ has been prepared (Appendix 17.10).

9.2.14.6 Reporting of SAEs

All SAEs experienced by a patient after informed consent has been obtained must be reported to the Sponsor and WWCT within 24 hours of the site's awareness of the event. A written summary fully documenting the event, in order to permit the Sponsor to file a report which satisfies regulatory guidelines, will follow within three calendar days. The event shall also be reported to the Institutional Review Board (IRB) in accordance with IRB reporting requirements in addition to the FDA and other Health Authorities within the timelines as per regional requirements.

The Sponsor commits to the FDA reporting requirements including:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to

this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)].

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin) [21 CFR 312.33].

10 CRITERIA FOR EVALUATION OF STUDY RESULTS

10.1 Criteria for Evaluation of Efficacy

10.1.1 Primary efficacy outcome

The primary efficacy outcome is the percentage of patients who experience one of the following events during the first 28 days:

- All-cause mortality
- Requirement for ICU admission and/or ventilatory support due to COVID-19
- CV complications*:
  - HF or
  - AMI or
  - myocarditis or
  - new sustained or symptomatic arrhythmia or
  - stroke

*see definitions in Appendix 17.8

10.1.2 Secondary efficacy evaluations

The secondary efficacy parameters are listed in section 4.1.4.

To control the family-wise Type I error rate, the Benjamini-Hochberg procedure will be applied.

10.1.3 Other efficacy evaluations

Other efficacy parameters are listed in section 4.1.5

The results of the findings for other endpoints are supportive and not confirmatory on their own. Therefore, the effect of the randomly allocated study treatment on the other efficacy endpoints are reported, in addition to measures of effect sizes, standard errors, confidence intervals, with nominal *p* values, unadjusted for testing multiplicity.

10.2 Criteria for Evaluation of Safety

The safety parameters of interest are listed in section 4.2.2.

10.3 Description of Patient Groups for Analyses

10.3.1 Intention-to-treat (ITT) Population

The primary analyses will be performed on the ITT population. All patients who were randomized will be included in the ITT analyses.

10.3.2 Per-Protocol Population

The Per-Protocol Set will be a subset of the ITT population who do not present with any major protocol deviations potentially impacting on the primary outcome and who must have a study treatment compliance of > 75%.

11 STATISTICAL METHODS

11.1 Sample Size Estimation

Assuming that 19% of patients qualifying for the study in the placebo group would develop one or more primary outcomes, a treatment effect of lowering the event rate by 50% (i.e., only 9.5% of patients treated with CardiolRx™ would experience a primary outcome event, a two-sided alpha of 0.05 and 80% power, 211 patients per group (422 in total) would be required.

Consideration will be given to adjust the sample size just before the interim analysis, should the observed event rate differ from the assumption above. Consideration will also be given to upgrading the Ordinal Outcome Scale first secondary endpoint to be the primary endpoint should the event rate of the current primary endpoint be significantly lower than the above assumption. This would be carried out in a blinded fashion. If the overall primary event rate is lower than (19 + 9.5)/2 = 14.25%, the sample size will be increased to preserve 80% power to detect a 50% relative reduction with a two-sided alpha of 0.05.

11.2 Efficacy Analyses

Descriptive statistics will be used to compare baseline characteristics between the two groups. Continuous variables will be expressed as mean ± SD, categorical variables will be expressed in counts with percentages.

11.2.1 Primary efficacy analysis

For the primary efficacy analysis, the proportions of patients experiencing at least one primary outcome event as described in section 10.1.1 in the active group will be compared to the proportions of patients experiencing at least one primary event in the placebo group using Fisher's exact test. The proportions will be expressed as percentages. In addition, the 95% confidence interval for the proportion using exact (Clopper-Pearson) estimates will be provided.

A secondary exploratory sensitivity analysis of the primary endpoint will compare time to the occurrence of the first primary event between the two groups using a Cox proportional hazards model. Kaplan-Meier plots for each treatment group will also be generated.

11.2.2 Secondary Efficacy Analyses

The first secondary efficacy analysis will be analyzed using the F-S test (Finkelstein and Schoenfeld 1999). This method compares each subject to every other subject in a pairwise manner following the ranking of the first secondary endpoint (Ordinal Outcome Scale):

1) not hospitalized and no limitations of activities;
2) not hospitalized, with limitation of activities, home oxygen requirement, or both;
3) hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care
4) hospitalized, not requiring supplemental oxygen but requiring ongoing medical care
5) hospitalized, requiring any supplemental oxygen;
6) hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices;
7) hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
8) MI or stroke diagnosed since randomization
9) Death

The F-S test is based on the sum of 'scores' of subjects in the CardiolRx™ group. Where the score is 1, -1 or 0 according to whether the subject is the winner, the loser or tied, respectively, according to the hierarchy above.

In addition, the CardiolRx™ to placebo Win ratio (WR) will be calculated, as described by Pocock.(Pocock et al. 2012) For this statistic, every subject in the CardiolRx™ group is compared to every subject in the placebo group in a pairwise manner following the ranking of the first secondary efficacy endpoint. The WR is the number of pairs with CardiolRx™ subject 'wins' divided by the number of pairs with placebo subject 'wins'. The associated 95% CI will bebased on the F-S test statistic to ensure consistency between the CI and the F-S test. A 95%CI for the WR entirely above 1 indicates a better outcome in the CardiolRx™ group.

Changes in hs-troponin and TNF-alpha from baseline to peak elevation during the 28-day treatment period between the two treatment groups will be analyzed using an ANCOVA with the baseline value as covariate.

Treatment effect estimates and 95% confidence intervals will be determined.

To control the family-wise Type I error rate, the Benjamini-Hochberg procedure will be applied to all secondary efficacy analyses.

11.2.3 Other Efficacy and Safety Analyses

The differences in continuous outcomes from baseline to 4 weeks post randomization between the two treatment groups will be analyzed using an ANCOVA. Treatment effect estimates and 95% confidence intervals will be determined.

Binary outcomes will be compared using Fisher's Exact test. The differences in proportions experiencing these outcomes will be estimated, along with 95% confidence intervals.

The elevation of hs-troponin, NT-proBNP, D-dimer and inflammatory markers over time from baseline to Day 7 will be compared using a ROC-AUC analysis, including data from all time points.

Win ratios for Ordinal Outcome Scale endpoint to 60 days after randomization will be analyzed as described above for the first secondary efficacy endpoint (Section 11.2.2).

Standard tests of the overall difference between treatment groups will be performed for the C-SSRS and the PICQ .

11.3 Interim Analysis

A formal interim analysis with respect to the primary endpoint will be carried out after approximately 50% of patients completed the 28-Day follow-up or terminated the study early. The purpose of this interim analysis is to detect potential harm early. After the results become available, the DSMC will make recommendations to the Steering Committee concerning safety concerns and the appropriateness of continuing the study following Stopping Guidelines in section 11.7 of this protocol.

11.4 Statistical Inference

P-value-based claims about the primary efficacy outcome will be based on $p<0.05$.

11.5 Planned Subgroup Analyses

Planned subgroup analyses for the primary endpoint include the following:

- Patient < 50 years of age vs. patients ≥ 50 years of age
- Males vs. females
- Baseline DM vs. no DM
- Baseline CVD vs. no CVD
- Baseline HF vs. no HF
- Baseline HTN vs. no HTN
- On dexamethasone vs. not on dexamethasone
- On remdesivir vs. not on remdesivir
- On baricitinib plus remdesivir vs. not on baricitinib plus remdesivir
- On convalescent plasma vs. not on convalescent plasma
- On any of these: dexamethasone, remdesivir, baricitinib plus remdesivir, convalescent plasma vs. not on any of these
- Treated with monoclonal antibody infusion before hospital admission versus not treated with monoclonal antibody infusion before hospital admission

These potential subgroup effects will be explored using a treatment-interaction test (test for homogeneity).

11.6 Missing Values

All attempts will be made to minimize missing follow-up data. Data that are collected only at baseline will not be imputed.

For missing primary and secondary outcome data a multiple imputation algorithm will be applied, using the technique of White et al. (White, Royston, and Wood 2011). This assumes the outcome is missing at random after taking into account the association of the outcome with baseline characteristics in patients with complete data. 25 consequent complete data sets will be generated and the combined treatment effect estimate, 95% confidence interval and P-value will be obtained using Rubin's rule.

For the primary outcome an additional tipping point analysis will be conducted should the above analysis be statistically significant at the 5% level, as follows.
For patients with missing outcome data a two-way display of all possible numbers with the primary outcome in each treatment group will have the consequent P-values calculated. Those with P above 0.05 will indicate the tipping points for which the positive primary analysis would be contradicted.

11.7 Stopping Guidelines

The DSMC will evaluate the results of the interim analysis after approximately 50% of patients have completed the 28-Day assessment (or terminated the study early) with

respect to prospectively defined criteria and make recommendations concerning safety concerns and the appropriateness of continuing the study.

Early stopping criteria:
The DSMC will recommend stopping the trial for safety reasons if there is a statistically significant imbalance of deaths in the active vs. the placebo group at a $p<0.05$ level, as determined by a two-sided Fisher's Exact test. In addition, the DSMC has the right to recommend stopping the trial early for evidence of harm that was not pre-defined by a formal stopping rule.

It is unlikely for the trial to stop early for overwhelming efficacy ($p<0.001$). Therefore, no stopping rule for superiority will be applied in order to collect sufficient data on secondary endpoints and evaluation of safety.

12 ORGANISATIONAL STRUCTURE

12.1 Sponsor

Cardiol Therapeutics Inc., 2265 Upper Middle Road, Suite 602, Oakville, Ontario, L6H 0G5 Canada will be the Sponsor of this study.

12.2 Project Management Team

The Sponsor will select qualified team members for a Project Management Team, responsible for overall study management, including preparation of all study material and procedures, safety reporting, data quality assurance as well as for the maintenance of the trial master file. The Project Management Team will also be responsible for organization of meetings, site initiation and training, on-site monitoring and study close-out and will issue regular progress reports and newsletters to be sent to investigators and committees. The members of the Project Team are listed in Appendix 17.9. WWCT will support the Project Management Team and will carry out tasks as described in the contractual agreement between WWCL and the Sponsor.

12.3 Data Management Centre

A Data Management Centre will be established at WWCT. WWCT will be responsible for preparing the e-CRF and the database as well as the database management, in-house data monitoring, data handling, cleaning and statistical reporting.

12.4 Steering Committee

A Steering Committee will be appointed, which will include the Study Chair and a minimum of four other clinicians. The Steering Committee will be responsible for providing clinical and methodological guidance, including overall study design, execution, analysis, and publication of the main study results. The Steering Committee will oversee the management of the clinical trial sites and will also act as the Publication Committee.

While the study is ongoing, the Committee will approve any protocol amendment that may become necessary and is responsible for maintaining the scientific integrity of the study. Steering Committee meetings may include representatives from the Sponsor and from the Data Management Centre.

The Steering Committee will receive recommendations from the Data Safety and Monitoring Committee (DSMC) regarding the appropriateness of continuing the study. The final decision will rest with the Steering Committee.

12.5 Data Safety and Monitoring Committee (DSMC)

An independent DSMC will be established. The committee will consist of at least two clinicians and a statistician who are not otherwise associated with the study. The DSMC will review all SAEs after 50 patients have completed the 28-Day assessment (or terminated the study earlier) and on an ongoing basis by treatment code.

The DSMC will also conduct unblinded reviews of the QTc intervals measured in the first 100 patients and make recommendations to the Steering Committee concerning safety concerns and the appropriateness of continuing the study.

The DSMC will evaluate the results of the interim analysis after approximately 50% of patients have completed the 28-Day assessment (or terminated earlier) with respect to prospectively defined criteria for declaring harm and futility, as documented in section 11.7 of this study protocol and in the DSMC Charter.

In addition, the DSMC has the right to recommend stopping the trial early for evidence of harm that was not pre-defined by a formal stopping rule.

12.6 Adjudication Committee

This Committee consists of at least three clinicians who have been appointed by the Steering Committee. The members of the Adjudication Committee will classify all SAEs to pre-specified definitions, as described in the Event Classification Manual, based on medical records and other documents. In addition, all endpoints will be verified by the Adjudication Committee.

13 DATA COLLECTION AND MONITORING

13.1 Case Report Forms (CRFs)

Electronic data capture will be used for this trial, meaning that all study data will be entered in electronic case report forms (eCRF) at the investigational site. Data collection will be completed by authorized study site personnel designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study site personnel prior to the study being initiated and any data being entered into the system for any study patients.

The study data will be housed on a secure in-house server at WWCT throughout the duration of study, and up to 10 years after the study is complete. An encrypted CD of the tabulated study data will be stored at the WWCT for 25 years after completion of the study.

13.2 Data Collection and Cleaning

13.2.1 Data collection

Records for all patients from whom an Informed Consent is obtained will be stored on a secure eCRF that will be maintained at the Data Management Centre. All eCRF corrections are to be made by an investigator or other authorized study site personnel. The investigator/co-investigator must confirm by his/her electronic signature in a specific section of the eCRF that he/she has reviewed the data, and that the data is complete and accurate.

13.2.2 Data validation

Data validation procedures will be described in detail in the Data Management Plan.

13.3 Monitoring

13.3.1 Virtual monitoring

The Project Management Team is responsible for monitoring according to applicable local GCP standards and ICH guidelines to ensure the completeness, correctness, and consistency of the data and to assess whether the study is executed according to this protocol. Specific items to be checked are listed in the Investigator's Study File.

To verify that the CRFs are completed accurately and in accordance with source documents, source data verification will be performed. The CRFs and related source documents will be reviewed in detail by the on-site monitor during each visit. Checks for completeness and correctness of the data will be done by comparing CRF entries with information in the patients' local medical records.

13.3.2 Data Review and Cleaning

In-house data review and cleaning will be performed by WWCT. In case of missing, erroneous or incomplete data, further information will be requested by WWCT via electronic Data Clarification Forms (eDCFs). These are sent directly to the investigator and copied to the monitor in charge of the site.

13.3.3 Audit/Inspection

The Sponsor, WWCT and/or a competent authority may perform audits. The auditor/inspector must have access to all study and source documentation, facilities and equipment used in this study. The Steering Committee will supervise audit procedures and is entitled to initiate audits on its own.

14 INVESTIGATOR RESPONSIBILITIES AND OBLIGATIONS

14.1 Declaration of Helsinki

The study will be carried out in accordance with the provisions of the Declaration of Helsinki (last revised version, see Appendix 17.1) and with applicable local GCP standards.

14.2 Local IRB/REB

According to local laws and regulations, the study protocol and the Patient ICF must be approved by a local IRB/REB for each participating center.

It is the responsibility of the investigator to submit the protocol for institutional review. A copy of the letter of approval from the local IRB/REB, with a content in accordance with local regulations, must have been received by the Project Management Team prior to shipment of study drugs to the investigational site. Major changes to the protocol, as well as a change of a principal investigator, must be approved by the local IRB/REB and documentation of this approval must be provided. Records of the local IRB/REB review and approval of all documents pertaining to this study must be kept on file by the investigator in the Investigator's Study File.

Apart from the investigational procedures specified in the protocol, investigators are not allowed to perform ancillary studies without written approval from the Steering Committee and the local IRB/REB.

14.3 Informed Consent and Patient Protection

14.3.1 Patient Informed Consent

It is an obligation of the investigator to obtain informed consent from the patient by means of a dated and signed ICF before any study-related procedure is performed. The ICF must be written in the local language in accordance with local laws and regulations.
'Informed consent' also implies individual discussion with the patient about the nature of study treatment and examinations to be conducted in a language that is easy to comprehend. The patient should fully understand that his/her refusal to participate in the study will not affect the quality of medical care. In addition, the patient must be informed that, without disclosing his/ her name, relevant medical data will be disclosed to the Project Management Team and WWCT that his/her medical records will be inspected during on-site monitoring, and may be inspected again by auditors and/or regulatory authorities.

Should a protocol amendment be made, the ICF may be revised to reflect the changes in the protocol. It is the responsibility of the investigator to ensure that an amended ICF is reviewed and approved by the local IRB/REB, and that it is signed by all patients subsequently entered in the study and those currently in the study, if affected by the amendment.

14.3.2 Patient data protection

The patients should be informed in writing that his/her medical data relevant to this study will be stored and analyzed while maintaining confidentiality in accordance with local data protection laws. All data transferred to the CRF and any process derived from the CRF will be handled anonymously. This will ensure that the identity of the individual will be protected.

The patient should also be informed in writing about the possibility of audits by authorized representatives of the Sponsor or the WWCT or a designee in which case a review of those parts of the hospital records relevant to the study may be required.

14.4 Study Protocol Adherence and Modifications

14.4.1 Protocol adherence

The protocol must be read thoroughly and the instructions must be followed exactly. The same applies to instructions given in the eCRF and to any additional instructions issued by the Project Management Team or WWCT. Whenever a deviation occurs in the interest of the patient's well-being, the on-site monitor must be informed and a course of action must be agreed upon. All deviations will be kept in the protocol deviation log.

14.4.2 Changes to protocol and related procedures

Changes to the protocol should only be made in the form of protocol amendments. If substantial changes to the design of the study are made, local IRBs/ERBs should be notified and, if required, approve the change before inclusion of new patients.
The Project Management Team is responsible for the distribution of a protocol amendment to investigators. Investigators are responsible for the distribution of an amendment to all staff involved in the study and to the local IRB/ERB.

14.5 Investigational Product Control

It is the investigator's responsibility to ensure that study drugs are stored in a secure area (locked, limited personnel access), and dispensed appropriately.

The investigator is responsible for maintaining accurate records of the dispensing of the study medication in a study drug accountability log.

All study drug supplies are for this protocol only and not for any other use. After completion of the study, all unused study materials must be destroyed on site.

14.6 Data Collection and Documentation

For every patient, the hospital or clinic file must clearly indicate that the patient has given informed consent and participates in the study. For all study assessments, the hospital or clinic file should include clinic visit and interim contact dates, records of vital signs, medical

history, clinical assessment findings, procedures performed and their findings, laboratory results, concomitant treatment, any AEs encountered and other notes as appropriate. This constitutes 'source data'. All entries on the eCRFs must be backed up by source data unless specified otherwise. Source data must be made available for perusal by the on-site monitor during a monitoring visit. In order to allow detection of inaccuracies in transcribing data from original records into the eCRF, all original laboratory reports must be kept available for review in the patient hospital or clinic file.

The CRFs must be kept in order and up-to-date so that they always reflect the latest observations on the patients enrolled in the study.

Each patient's study file should have attached to it the original signed ICF. When the study is completed, the ICF should be kept on file with a copy of the completed eCRF in the study file provided, or a note should be made indicating where the study records can be located. All records should be kept in accordance with applicable national laws and regulations.

14.7 Reporting of AEs and SAEs

It is a regulatory obligation of the investigator and her/his staff to record and report any serious clinical event or adverse experience that occurs while a patient is participating in this study. Detailed instructions for AE and SAE reporting are given in section 9.2.14 of this protocol. The instructions given in this section must be observed closely. Non-compliance is a serious protocol violation and may lead to the closure of the center involved.

If required by local regulations, the investigator must also inform the local IRB/ERB about SAEs.

14.8 Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories (1) investigator's study file, and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, case report and query forms, Ethics Review Board and governmental approval (if required) with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc.

The patient's clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG and special assessment reports, signed ICF(s) , consultant letters, and patient screening and enrolment logs. The investigator must keep these two categories of

documents on file after completion or discontinuation of the study according to local requirements.

Should the investigator wish to assign the study records to another party or move them to another location, The Project Management Team must be notified in advance.

Where source documents are required for the continued care of the patient, appropriate copies should be made.

14.9 Confidentiality of Trial Documents and Patient Records

The investigator must assure that patient anonymity will be maintained and that their identities shall be protected from unauthorized parties. On eCRFs or other documents submitted to WWCT and/or to the Sponsor, patients should not be identified by their names, but by an identification code. The investigator should keep a patient enrolment log relating codes to the names of patients. The investigator should maintain documents that are not for submission to WWCT and/or the Sponsor in strict confidence.

14.10 Direct Access to Source Data/Documents

The investigator shall supply the Project Management Team and WWCT on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data entry are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

14.11 Trial Network Registration

The study is registered on http://clinicaltrials.gov.

15 STUDY TIMELINES

Eligible patients will be randomized and will be followed for 60 days. We estimate the following: a recruitment period of 9 months, follow-up 2 months, time for data collection and cleaning 2 months, database lock, analysis and reporting 2 months, resulting in a total study time of approximately 15 months.

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17 APPENDICES

17.1 Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
for
Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
and the
Washington DC 2002 clarification on Paragraph 29

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patients interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable

and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subject should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidently of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subjects freely- given informed consent preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of the relationship.
24. For a research subject who is legally incompetent physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available, Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. 'This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the, study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods, do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

FOOTNOTE: NOTE OF CLARIFICATION ON PARAGRAPH 29 of the WMA DECLARATION OF HELSINKI

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

17.2 Schedule of Study Procedures

17.2.1 Clinical Assessments

	Study Days[6]								
	0-1	3	5	7	14	21	28	45	60
Consent	X								
Clinical assessment	X			X	X	X	X	X	X
Demographics	X								
Medical History	X								
Vital Signs[1]	X	X	X	X	X	X	X	X	X
Chest X-ray	X						X		
ECG	X	X	X	X	X	X	X		
Echocardiography	X						X		
Columbia-Suicide Severity Rating Scale	X						X		
Patient Impression of Change Questionnaire							X		X
Ordinal Outcome Scale	X	X	X	X	X	X	X	X	X
CMR (subset of patients at selected sites)							X	(X)[7]	
Randomization[2]	X								
Study medication[3]	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX								
Study drug dose adjustment /accountability[4]		X	X	X	X	X	X		X
Concomitant Medication	X	X	X	X	X	X	X	X	X
AE/SAE recording[5]	X	X	X	X	X	X	X	X	X

[1] Vital signs include heart rate and blood pressure; weight at baseline and at days 7, 14, 21, 28, 45 and 60; height at baseline
[2] Randomization on Day 1 after all baseline assessments, including local laboratory tests, have been completed, within 96 hours of hospital admission (or waiting for planned admission for <96 hours)
[3] Start of study drug after randomization in the evening of Day 1, according to treatment schedule
[4] At final visit accountability only
[5] Adverse Event recording starts after informed consent is obtained
[6] After hospital discharge, all scheduled assessments will be carried out as out-patient visits or home visits up to Day 7. After Day 7, all visits will be out-patient visits.
[7] If CMR on Day 28 was not possible

17.2.2 Laboratory Assessments

	Study Days[6]								
	0-1	3	5	7	14	21	28	45	60
Local Laboratory[7]									
CBC	X			X	X		X		
ALT/AST	X			X	X		X		
Alkaline Phosphatase	X			X	X		X		
Bilirubin	X			X	X		X		
Creatinine/ eGFR	X			X	X		X		
INR	X			X	X		X		
Pregnancy test[8]	X								
Glucose	X								
Total cholesterol	X								
Lymphocyte count	X			X	X		X		
LDH	X			X	X		X		
Central Laboratory[9]									
Hs-troponin	X	X	X	X			X		
NT-proBNP	X	X	X	X			X		
D-dimer	X	X	X	X			X		
Hs-CRP	X	X	X	X			X		
Ferritin	X	X	X	X			X		
IL-6,	X	X	X	X			X		
IL-10	X	X	X	X			X		
IL-1 beta	X	X	X	X			X		
TNF-alpha	X	X	X	X			X		
Retention of frozen samples for future testing	X	X	X	X			X		
Retention of frozen samples for CBD levels	X	X	X	X			X		

[6] After hospital discharge, all scheduled assessments will be carried out as out-patient or home visits up to Day 7. After Day 7, all visits will be out-patient visits.
[7] All local laboratory assessments at baseline, to be performed before randomization on Day 0-1
[8] Serum pregnancy test (hCG) in women with child-bearing potential only
[9] Retention of frozen samples for central laboratory analyses

17.3 Patient Impression of Change Questionnaire

Since the start of this study, my overall status is:

√ one box only:

[ ]	[ ]	[ ]	[ ]	[ ]
Much Improved	Improved	No Change	Worse	Much Worse

17.4 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version
Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:
This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

PART 1 OF 5

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

☐ Section below not applicable		
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

PART 2 OF 5

☐ Section below not applicable

INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

PART 3 OF 5

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Have you made a suicide attempt? ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?***	Total # of Attempts _____	Total # of Attempts _____
Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:		
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

PART 4 OF 5

☐ Section below not applicable

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

Following must be answered

Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

PART 5 OF 5

☐ Section below not applicable

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

CARDIOL THERAPEUTICS

17.5 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – SINCE LAST VISIT VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit
Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:
This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

PART 1 OF 5

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐

☐ Section below not applicable

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it"*. ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them"*. ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

PART 2 OF 5

☐ Section below not applicable

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____

Type # (1-5)	***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day		____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous		____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts		____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply		____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply		____

PART 3 OF 5

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐

PART 4 OF 5

☐ Section below not applicable

Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐

Following must be answered

Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐

PART 5 OF 5

☐ Section below not applicable

Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

17.6 Drugs that can prolong QTc intervals

COMBINED LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES (TDP)

CredibleMeds®

CredibleMeds® has reviewed available evidence for the drugs on the following list and place them in one of three designated categories: Known Risk of TdP (KR), Possible Risk of TdP (PR) or have a Conditional Risk of TdP (CR). The full description of these categories can be found on the CredibleMeds.org website.

Generic Name	Brand Name
Abarelix (PR)	Plenaxis
Abiraterone (CR)	Zytiga and others
Aclarubicin (KR)	Aclacin and others
Alfuzosin (PR)	Uroxatral
Alimemazine (Trimeprazine) (PR)	Nedeltran and others
Amantadine (CR)	Symmetrel and others
Amiodarone (KR)	Cordarone and others
Amisulpride (CR)	Barhemsys and others
Amitriptyline (CR)	Elavil (Discontinued 6/13) and others
Amphotericin B (CR)	Fungilin and others
Amsacrine (Acridinyl anisidide) (CR)	Amsidine
Anagrelide (KR)	Agrylin and others
Apalutamide (PR)	Erleada
Apomorphine (PR)	Apokyn and others
Aripiprazole (PR)	Abilify and others
Arsenic trioxide (KR)	Trisenox
Artemether/Lumefantrine (PR)	Coartem
Artenimol/piperaquine (PR)	Eurartesim
Asenapine (PR)	Saphris and others
Astemizole (KR)	Hismanal
Atazanavir (CR)	Reyataz and others
Atomoxetine (PR)	Strattera

Generic Name	Brand Name
Azithromycin (KR)	Zithromax and others
Bedaquiline (PR)	Sirturo
Bendamustine (PR)	Treanda and others
Bendroflumethiazide (Bendrofluazide) (CR)	Aprinox and others
Benperidol (PR)	Anquil and others
Bepridil (KR)	Vascor
Betrixaban (PR)	Bevyxxa
Bortezomib (PR)	Velcade and others
Bosutinib (PR)	Bosulif
Buprenorphine (PR)	Butrans and others
Cabozantinib (PR)	Cometriq
Capecitabine (PR)	Xeloda
Carbetocin (PR)	Pabal and others
Ceritinib (PR)	Zykadia
Cesium Chloride (KR)	Energy Catalyst
Chloral hydrate (CR)	Aquachloral and others
Chloroquine (KR)	Aralen
Chlorpromazine (KR)	Thorazine and others
Chlorprothixene (KR)	Truxal
Cilostazol (KR)	Pletal
Cimetidine (CR)	Tagamet
Ciprofloxacin (KR)	Cipro and others

Generic Name	Brand Name
Cisapride (KR)	Propulsid
Citalopram (KR)	Celexa and others
Clarithromycin (KR)	Biaxin and others
Clofazimine (PR)	Lamprene
Clomipramine (CR)	Anafranil
Clotiapine (PR)	Entumine
Clozapine (PR)	Clozaril and others
Cobimetinib (PR)	Cotellic
Cocaine (KR)	Cocaine
Crizotinib (PR)	Xalkori
Cyamemazine (Cyamepromazine) (PR)	Tercian
Dabrafenib (PR)	Tafinlar
Dasatinib (PR)	Sprycel
Degarelix (PR)	Firmagon and others
Delamanid (PR)	Deltyba
Desipramine (PR)	Pertofrane and others
Deutetrabenazine (PR)	Austedo
Dexmedetomidine (PR)	Precedex and others
Dextromethorphan/Quinidine (PR)	Nuedexta
Diphenhydramine (CR)	Benadryl and others
Disopyramide (KR)	Norpace
Dofetilide (KR)	Tikosyn

If list is printed, check website at www.crediblemeds.org • Please see Disclaimer below • List continued over

Generic Name	Brand Name
Dolasetron (PR)	Anzemet
Domperidone (KR)	Motilium and others
Donepezil (KR)	Aricept
Doxepin (CR)	Sinequan and others
Dronedarone (KR)	Multaq
Droperidol (KR)	Inapsine and others
Efavirenz (PR)	Sustiva
Eliglustat (PR)	Cerdelga
Encorafenib (PR)	Braftovi
Entrectinib (PR)	Rozlytrek
Eperisone (CR)	Myonal and others
Epirubicin (PR)	Ellence and others
Eribulin mesylate (PR)	Halaven
Erythromycin (KR)	E.E.S. and others
Escitalopram (KR)	Cipralex and others
Esomeprazole (CR)	Nexium and others
Ezogabine (Retigabine) (PR)	Potiga and others
Famotidine (CR)	Pepcid and others
Felbamate (PR)	Felbatol
Fingolimod (PR)	Gilenya
Flecainide (KR)	Tambocor and others
Fluconazole (KR)	Diflucan and others
Fluorouracil (5-FU) (PR)	Adrucil and others
Fluoxetine (CR)	Prozac and others
Flupentixol (PR)	Depixol and others
Fluvoxamine (CR)	Faverin and others
Furosemide (frusemide) (CR)	Lasix and others
Galantamine (CR)	Reminyl and others

Generic Name	Brand Name
Garenoxacin (CR)	Geninax
Gatifloxacin (KR)	Tequin
Gemifloxacin (PR)	Factive
Gilteritinib (PR)	Xospata
Glasdegib (PR)	Daurismo
Granisetron (PR)	Kytril and others
Grepafloxacin (KR)	Raxar
Halofantrine (KR)	Halfan
Haloperidol (KR)	Haldol and others
Hydrochlorothiazide (CR)	Apo-Hydro and others
Hydrocodone - ER (PR)	Hysinglaâ„¢ ER and others
Hydroquinidine (Dihydroquinidine) (KR)	Serecor
Hydroxychloroquine (KR)	Plaquenil and others
Hydroxyzine (CR)	Atarax and others
Ibogaine (KR)	
Ibutilide (KR)	Corvert
Iloperidone (PR)	Fanapt and others
Imipramine (Melipramine) (PR)	Tofranil
Indapamide (CR)	Lozol and others
Inotuzumab ozogamicin (PR)	Besponsa
Isradipine (PR)	Dynacirc
Itraconazole (CR)	Sporanox and others
Ivabradine (CR)	Procoralan and others
Ivosidenib (PR)	Tibsovo
Ketanserin (PR)	Sufrexal
Ketoconazole (CR)	Nizoral and others
Lacidipine (PR)	Lacipil and others
Lansoprazole (CR)	Prevacid and others

Generic Name	Brand Name
Lapatinib (PR)	Tykerb and others
Lefamulin (PR)	Xenleta
Lenvatinib (PR)	Lenvima
Leuprolide (Leuprorelin) (PR)	Lupron and others
Levofloxacin (KR)	Levaquin and others
Levomepromazine (Methotrimeprazine) (KR)	Nosinan and others
Levomethadone (levamethadone) (PR)	
Levomethadyl acetate (KR)	Orlaam
Levosulpiride (KR)	Lesuride and others
Lithium (PR)	Eskalith and others
Lofexidine (PR)	Lucemyra
Loperamide (CR)	Imodium
Lopinavir/Ritonavir (PR)	Kaletra and others
Lumateperone (PR)	Caplyta
Lurasidone (PR)	Latuda
Maprotiline (PR)	Ludiomil
Melperone (PR)	Bunil and others
Memantine (PR)	Namenda XR
Mesoridazine (KR)	Serentil
Methadone (KR)	Dolophine and others
Metoclopramide (CR)	Reglan and others
Metolazone (CR)	Zytanix and others
Metronidazole (CR)	Flagyl
Mianserin (PR)	Tolvon
Midostaurin (PR)	Rydapt
Mifepristone (PR)	Korlym and others
Mirabegron (PR)	Myrbetriq
Mirtazapine (PR)	Remeron

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Generic Name	Brand Name
Moexipril/Hydrochlorothiazide (PR)	Uniretic and others
Moxifloxacin (KR)	Avelox and others
Necitumumab (PR)	Portrazza
Nelfinavir (CR)	Viracept
Nicardipine (PR)	Cardene
Nifekalant (KR)	Shinbit
Nilotinib (PR)	Tasigna
Norfloxacin (PR)	Noroxin and others
Nortriptyline (PR)	Pamelor and others
Nusinersen (PR)	Spinraza
Ofloxacin (PR)	Floxin
Olanzapine (CR)	Zyprexa and others
Omeprazole (CR)	Losec and others
Ondansetron (KR)	Zofran and others
Osilodrostat (PR)	Isturisa
Osimertinib (PR)	Tagrisso
Oxaliplatin (KR)	Eloxatin
Oxytocin (PR)	Pitocin and others
Paliperidone (PR)	Invega and others
Palonosetron (PR)	Aloxi
Panobinostat (PR)	Farydak
Pantoprazole (CR)	Protonix and others
Papaverine HCl (Intra-coronary) (KR)	
Paroxetine (CR)	Paxil and others
Pasireotide (PR)	Signifor
Pazopanib (PR)	Votrient
Pentamidine (KR)	Pentam
Perflutren lipid microspheres (PR)	Definity and others
Perphenazine (PR)	Trilafon and others
Pilsicainide (PR)	Sunrythm
Pimavanserin (PR)	Nuplazid
Pimozide (KR)	Orap
Pipamperone (PR)	Dipiperon and others

Generic Name	Brand Name
Piperacillin/Tazobactam (CR)	Tazosyn and others
Pitolisant (Tiprolisant) (PR)	Wakix
Posaconazole (CR)	Noxafil and others
Pretomanid (PR)	
Primaquine phosphate (PR)	
Probucol (KR)	Lorelco
Procainamide (KR)	Pronestyl and others
Promethazine (PR)	Phenergan
Propafenone (CR)	Rythmol SR and others
Propofol (KR)	Diprivan and others
Prothipendyl (PR)	Dominal and others
Quetiapine (CR)	Seroquel
Quinidine (KR)	Quinaglute and others
Quinine sulfate (CR)	Qualaquin and others
Ranolazine (CR)	Ranexa and others
Ribociclib (PR)	Kisqali
Rilpivirine (PR)	Edurant and others
Risperidone (CR)	Risperdal
Romidepsin (PR)	Istodax
Roxithromycin (KR)	Rulide and others
Rucaparib (PR)	Rubraca
Saquinavir (PR)	Invirase(combo)
Selpercatinib (PR)	Retevmo
Sertindole (PR)	Serdolect and others
Sertraline (CR)	Zoloft and others
Sevoflurane (KR)	Ultane and others
Siponimod (PR)	Mayzent
Solifenacin (CR)	Vesicare
Sorafenib (PR)	Nexavar
Sotalol (KR)	Betapace and others
Sparfloxacin (KR)	Zagam
Sulpiride (KR)	Dogmatil and others
Sultopride (KR)	Barnetil and others

Generic Name	Brand Name
Sunitinib (PR)	Sutent
Tacrolimus (PR)	Prograf and others
Tamoxifen (PR)	Nolvadex and others
Tazemetostat (PR)	Tazverik
Telaprevir (CR)	Incivo and others
Telavancin (PR)	Vibativ
Telithromycin (PR)	Ketek
Terfenadine (KR)	Seldane
Terlipressin (KR)	Teripress and others
Terodiline (KR)	Micturin and others
Tetrabenazine (PR)	Nitoman and others
Thioridazine (KR)	Mellaril and others
Tiapride (PR)	Tiapridal and others
Tipiracil/Trifluridine (PR)	Lonsurf
Tizanidine (PR)	Zanaflex and others
Tolterodine (PR)	Detrol and others
Toremifene (PR)	Fareston
Torsemide (Torasemide) (CR)	Demadex and others
Tramadol (PR)	Crispin and others
Trazodone (CR)	Desyrel and others
Trimipramine (PR)	Surmontil and others
Tropisetron (PR)	Navoban and others
Valbenazine (PR)	Ingrezza
Vandetanib (KR)	Caprelsa
Vardenafil (PR)	Levitra
Vemurafenib (PR)	Zelboraf
Venlafaxine (PR)	Effexor and others
Voriconazole (CR)	VFend
Vorinostat (PR)	Zolinza
Ziprasidone (CR)	Geodon and others
Zotepine (PR)	Losizopilon and others
Zuclopenthixol (Zuclopentixol) (PR)	Cisordinol and others

N[illegible] based on this list are [illegible] basis to assure [illegible] able evidence [illegible] continued placement on this list. Because the list changes regularly, we re[illegible]org for the most up-to-date information. Most drugs have multiple brand names and it is not practical to list them on this form. The CredibleMeds.org website provides a partial list of the more common brands.

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Generated: August 11, 2020. List last revised: May 12, 2020

17.7 Drugs that are strong inducers of CYP3A4 and CYP2C19

17.7.1 CYP3A4 Inducers

- Anticonvulsants Phenytoin and Carbamazepine
- Testosterone receptor inhibitors Apalutamide and Enzulutamide
- Adrenal cortex hormone inhibitor Mitotane
- Antibiotic Rifampin
- St John's Wort
- Possibly Phenobarbital

17.7.2 CYP2C19 Inducers

- Rifampin

17.8 Definitions of Primary Outcomes

17.8.1 Requirement for ICU Admission and/or Ventilatory Support

An ICU admission will have occurred if the decision was made and the medical order written for transfer to ICU. Ventilatory support is only indicated if the oxygen saturation is <94% and can include new or recurrent requirement for any of the following:

a. supplemental oxygen by face mask
b. supplemental oxygen by nasal canula(e)
c. continuous positive pressure (CPAP) ventilation
d. endotracheal intubation and mechanical ventilation
e. extracorporeal membrane oxygenation (ECMO)

Normally, oxygen by nasal prongs should not be considered respiratory support unless there is documented hypoxemia (oxygen saturation < 94%).

17.8.2 Heart Failure (HF)

A Heart Failure Event includes the development of heart failure symptoms and signs
a. while in hospital or
b. requiring re-admission to hospital (for HF) or
c. requiring an urgent outpatient visit for HF

a) Heart Failure event while in hospital is defined by the following criteria:

1) The patient exhibits documented new or worsening symptoms due to HF, including at least ONE of the following:

    a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
    b. Decreased exercise tolerance
    c. Fatigue
    d. Other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol)

2) The patient has objective evidence of new or worsening HF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including:

    a. Physical examination findings considered to be due to heart failure, including new or worsened:

        i. Peripheral edema
        ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
        iii. Pulmonary rales/crackles/crepitations
        iv. Increased jugular venous pressure and/or hepatojugular reflux
        v. S_3 gallop

vi. Clinically significant or rapid weight gain thought to be related to fluid retention

b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:

i. Increased B-type natriuretic peptide (BNP) / N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 150 pg/mL or NT-proBNP > 600 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.

ii. Radiological evidence of pulmonary congestion

iii. Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure. For example, echocardiographic criteria could include: mitral valve septal or lateral E/e' > 15 or > 12, respectively;

iv. Echocardiographically demonstrated significant (>0.10) decrease in LVEF

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

3) The patient receives at least ONE of the following treatments specifically for HF:

a. Significant augmentation in oral diuretic therapy (e.g., doubling of loop diuretic dose, initiation of maintenance loop diuretic therapy, initiation of combination diuretic therapy)
b. Initiation of intravenous diuretic (even a single dose) or vasoactive agent (e.g., inotrope, vasopressor, vasodilator)
c. Mechanical or surgical intervention, including:
   i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
   ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

Combination diuretic therapy could include 1) a thiazide-type diuretic (e.g., hydrochlorothiazide, metolazone, chlorothiazide) plus a loop diuretic; or 2) mineralocorticoid receptor antagonist (MRA) (e.g., spironolactone or eplerenone) plus a loop diuretic.

b) Re-admission to hospital requires the following:

1) The patient is re-admitted to the hospital with a *primary diagnosis* of HF

2) The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)

3) Plus all of the features noted above for the diagnosis of HF

c) Urgent outpatient Heart Failure Visit

This category is for study patients who have been discharged from hospital, but require urgent treatment in clinic or in the ER for heart failure.

An Urgent Heart Failure Visit is defined as an event that meets all of the following:

1) The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization
2) The patient has the symptoms and signs (physical examination findings/laboratory evidence) of HF
3) The patient receives at least ONE of the following treatments specifically for HF:

    a. Initiation of intravenous diuretic or vasoactive agent (e.g., inotrope, vasopressor, or vasodilator)
    b. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
    c. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

Note that:

- significant augmentation of oral diuretic therapy will NOT be sufficient to fulfill the urgent HF visit criteria.

- clinic visits for *scheduled* administration of HF therapies or procedures (e.g., intravenous diuretics, intravenous vasoactive agents, or mechanical fluid removal) do NOT qualify as non-hospitalized HF events.

17.8.3 Acute Myocardial Infarction

17.8.3.1 General Considerations

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

17.8.3.2 Clinical Presentation

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with chronic or transient elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, HF, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

17.8.3.3 Biomarker Elevations

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. In general, troponins are preferred. CK-MB should be used if troponins are not available, and total CK may be used in the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL.

17.8.3.4 ECG Changes

Electrocardiographic changes can be used to support or confirm a MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

<u>ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):</u>

- ST elevation: New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women
- ST Depression and T-wave changes: New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or new T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

<u>Criteria for pathological Q-wave:</u>

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, and aVF)[a]

[a]The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

ECG changes associated with prior myocardial infarction:

- Pathological Q-waves, as defined above
- R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

Criteria for prior myocardial infarction (e.g., silent MI) - any of the following:

- Pathological Q waves with or without symptoms in the absence of non-ischemic causes
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a prior MI

ST-Segment Elevation MI (STEMI) versus Non-ST-segment Elevation MI (NSTEMI)

All events meeting criteria for MI* will also be classified as either ST-segment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), or unknown.

- **STEMI** – To be classified as a STEMI the event must meet all of the above criteria for myocardial infarction and one of the four criteria below.
    - New ST segment elevation at the J point in ≥2 contiguous leads, defined as: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads. Subjects must have an interpretable ECG (i.e., without evidence of left ventricular hypertrophy or pre-existing left bundle branch block), *or*
    - New left bundle branch block

- **NSTEMI** – To be classified as a NSTEMI the event must meet all of the above criteria for myocardial infarction and not meet criteria for classification as STEMI. In order to be classified as NSTEMI there must be adequate interpretable ECG documentation associated with the event.

- **Unknown** – Events which meet criteria as specified above for MI but do not meet criteria for STEMI or NSTEMI. All cases where ECG documentation of the acute event is missing, inadequate, or uninterpretable should be classified as Unknown.

Criteria for universal classification of myocardial infarction

Type 1:Spontaneous myocardial infarction

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to an ischemic imbalance

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-

arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable

Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarkers could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤99^{th} percentile URL) or a rise of cTn values ≥20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 4c: Myocardial infarction related to restenosis

Restenosis is defined as ≥50% stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values >99th percentile URL and no other significant obstructive CAD of greater severity following: (i) initially successful stent deployment or (ii) dilatation of a coronary artery stenosis with balloon angioplasty (<50%).

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Note: As noted above, although language states troponin, CKMB can be used with similar cut points.

17.8.4 Myocarditis

17.8.4.1 Definition of Myocarditis

Clinical criteria - symptoms of chest pain, arrhythmia or development of HF (as defined above) associated with elevated troponin and ECG changes in the absence of hemodynamically significant CAD* (defined as a stenosis greater than 50% in a major epicardial coronary artery) within the previous 90 days. Typically, this presentation is associated with the presence of – or with a history of a recent - viral infection.

In some situations, the diagnosis might be confirmed by one of the following:

- CMR diagnosis: (Lake Louise II Criteria) ***OR***
- Endomyocardial biopsy (if clinically indicated), showing either cellular inflammation and/or immunohistochemistry consistent with inflammation

*thorough evaluation of ischemia by coronary angiography, CT angiography and/or stress test; imaging is at the discretion of the PI but may not be feasible in the presence of COVID-19.

17.8.5 New sustained or symptomatic Arrhythmia

The development of any of the following arrhythmias are considered significant for the patients in this study. The rhythm must be documented by ECG or monitor strip.

- Sinus bradycardia – persistent HR less than 50/minute
- Atrio-ventricular Block – Mobitz Type I
  Mobitz Type II
  Complete AV block
- Atrial tachycardia – regular tachycardia with visible P waves sustained for more than 30 seconds. This may be paroxysmal (PAT) or become sustained
- Atrial flutter – atrial rate of 200 – 400 /min
- Atrial fibrillation (AF) – irregularly irregular narrow QRS complex arrhythmia
  - Paroxysmal AF – episode of AF lasting at least 30 seconds
  - Persistent AF: – with uncontrolled ventricular response (>100 beats/min)
    - with controlled ventricular response (<100 beats/min)
- Ventricular Premature Complexes
  - Monomorphic >10/min
  - Polymorphic >10/min
- Ventricular Tachycardia with HR greater than 100/min
- Ventricular fibrillation
- Ventricular asystole –cardiac standstill

17.8.6 Stroke

17.8.6.1 Ischemic Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

17.8.6.2 Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

17.8.6.3 Undetermined Stroke

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

17.8.6.4 Stroke Disability

Disability should be measured by a reliable and valid scale in all cases, typically at each visit and at 60 days post randomization. For example, the modified Rankin Scale may be used to address this requirement

Scale	Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

17.9 Project Management Team Members

Name	Title
Andrew Hamer, MD	Chief Medical Officer
Andrea B. Parker, MSc., PhD	Director, Clinical Affairs
Anthony Bolton, PhD	Director of Research
Bernard Lim, BSc., CEng, MIET, MIEEE	Chief of Operations
David Elsley, MBA	Chief Executive Officer
Anne Tomalin, BA, BSc, RAPS	Director, Regulatory Affairs
Kelly Narine, PhD	Director Medical Affairs

17.10 Cannabidiol and Drug-Drug Interactions for Patients with COVID-19

Notes:

1. Cannabidiol is a strong inhibitor of a number of CYP and UGT isoforms. Medications that depend on one (or more) of these enzyme isoforms for metabolism (that is, medications serve as a substrate for the enzyme) may then have slowed metabolism, thereby resulting in increased blood levels of the drug. For some drugs (particularly those with a narrow therapeutic index), this may result in toxicity.
2. The drugs listed are those that serve as a substrate for one or more of CYP2C8, CYP2C9, CYP2C19, CYP1A2, CYP2B6, UGT1A9 and UGT2B7.
3. Please note that certain drugs that are substrates for these enzymes are also strong inducers of CYP3A4 and therefore are exclusion criteria for this study, as depicted in **Appendix 17.7.**
4. Drugs listed in the table are arranged as follows: cardiovascular drugs, diabetes care drugs and then other commonly used drugs (in alphabetical order). The CYP or UGT isoform for which the drugs serve as a substrate are listed in the final column.
5. Many drugs serve as a substrate for more than one CYP or UGT isoform. They have only been recorded once in the table.
6. Undoubtedly, this patient population will be taking a wide spectrum of medication. If a medication of interest is not included in this list, please refer to a respected website such as DrugBank (www.drugbank.ca) to determine likelihood of drug-drug interaction.

Drug Class	Drug Name	Signs/Monitoring/Mitigation Strategies	Enzyme
Cardiovascular Drugs			
Diuretic	Torasemide	May cause hypotension, hypokalemia, increased creatinine - Monitor body weight and renal function. Adjust dose accordingly	CYP2C8
	Triamterene	May cause hyperkalemia, hyponatremia, nausea and vomiting, diarrhea, kidney stones – monitor potassium, adjust dose or change to other diuretic	CYP1A2
Statin	Cerivistatin Atorvastatin Fluvastatin Imvastatin Pitavastatin Lovastatin	May cause muscle breakdown, muscle pain, Monitor cholesterol level and review adverse effect profile - Adjust dose or substitute another agent	CYP2C8
	Rosuvastatin	As above. Rarely causes memory loss/confusion	CYP2C9
	Simvastatin	May cause muscle damage – adjust dose or substitute other medication	CYP2C19
Other Cholesterol lowering agents	Ezetimibe	Usually used in combination with a statin. May cause joint pain, muscle breakdown, diarrhea, increased upper respiratory tract infections –	UGT1A9

		monitor cholesterol, adjust dose or use another agent	
	Gemfibrozil	May cause angioedema, muscle breakdown, liver damage – monitor cholesterol, liver enzymes. Adjust dose or use another agent	UGT1A9
Anticoagulant	Warfarin	Monitor INR - Adjust dose if needed	CYP2C8
	Apixiban	An oral anticoagulant (NOAC) which is Xa inhibitor. Can cause bleeding – if bleeding not controlled, reverse with anti-Xa agent	CYP2C8
	Dabigitran	May cause bleeding, allergic reactions, gastritis – monitor clotting and adjust dose	UGT1A9
Anti-platelet	Clopidogrel	Bruising, bleeding – adjust dose	CYP2C9
	Cilostazol	May cause headache, dizziness or diarrhea – adjust dose or change medication	CYP2C19
Anti-arrhythmic	Amiodarone	Monitor QTc, Measure blood levels - adjust dose	CYP2C8
	Quinidine	Not used often. Prolongs QTc and can cause digoxin toxicity. Causes diarrhea, gastric upset, ringing in ears, liver toxicity, auto-immune responses – monitor carefully and either decrease dose or discontinue medication	CYP2C9
	Lidocaine	Blocks sodium channels. May cause bradycardia, drowsiness, tingling,	CYP1A2

		numbness – when used as anti-arrhythmic, dose can be carefully controlled	
	Mexilitine	Blocks sodium channels. May cause nausea, drowsiness, skin reactions – monitor CG, adjust dose	CYP1A2
	Propafenone	Blocks sodium channels. May cause hypersensitivity reactions, dizziness, GI upset and rarely agranulocytosis – monitor ECG, adjust dose or change to other agent	CYP1A2
	Disopyramide	Blocks sodium channels. May cause urinary retention, hypotension, worsening heart failure, aggravate glaucoma – monitor ECG, adjust dose or use another agent	CYP1A2
	Tocainide	Blocks sodium channels. May cause dizziness, nausea, paresthesia, tremor. DD interactions common – monitor ECG, reduce dose or change to another agent	CYP1A2
	Flecainide	Blocks sodium channels. May cause dizziness, fatigue, worsen HF – monitor ECG, adjust dose	CYP1A2
Calcium Channel Blocker	Verapamil Diltiazem Nicardipine	May cause headache, bradycardia, edema, constipation, worsening HF - Reduce dose as needed	CYP2C8
	Nifedipine	May cause edema, cough, hypotension – adjust dose or use another agent	CYP1A2
Angiotensin receptor blocker	Irbesartan	May cause hypotension, muscle pains, angioedema –	CYP2C8

		reduce dose/change medication	
	Candesarten Valsarten Losarten	Can cause hypotension/volume depletion – adjust dose	CYP2C9
Anti-anginal	Perhexiline	Perhexiline is a pFOX inhibitor used in some countries for severe angina. It has complex metabolism and difficult to use	CYP2B6
Beta Blockers	Carvedilol	Bradycardia, tiredness, bronchospasm – reduce dose or suspend	CYP2C9
	Timolol Propranolol	Timolol may be used for glaucoma. Can cause tiredness, SOB, worsening of asthma – adjust dose or change to another medication	CYP2C19
	Betaxolol	May cause bradycardia, nausea, constipation, unpleasant dreams and increase severity of asthma – adjust dose or change to other agent.	CYP1A2
Anti-hypertensives	Doxazosin	Hypotension, drowsiness, priapism - adjust dose	CYP2C9
	Clonidine (Alpha-2 agonist)	May cause dry mouth, dizziness, drowsiness, arrhythmia, and even confusion – Adjust dose or change to another agent	CYP1A2
	Labetalol (Alpha & Beta adrenergic blocker)	Primarily used to treat hypertension. May cause hypotension, fatigue, dizziness, bronchospasm –	UGT1A9

		monitor BP, adjust dose or change to other medication	
Peripheral Arterial Disease	Pentoxyphylline	May cause tachycardia, headache, dizziness, gastric upset – adjust dose or use another agent	CYP1A2
Pulmonary anti-hypertensive	Bosentan	Hypotension, headache, transaminase elevation, edema, anemia, pulmonary veno-occlusive disease – requires close monitoring of co-administered drugs for DD interactions.	CYP2C9
	Ambrisentan	Used to treat primary pulmonary hypertension. It is teratogenic if taken during pregnancy. Has limited usage	UGT1A9
PD5 Inhibitor	Sildenafil	Hypotension, tachycardia - Avoid nitrates, adjust dose or change to another agent	CYP2C9
Drugs for Diabetes Care			
Hypoglycemic	Rosiglitizone Tolbutamide Troglitazone Gliquidone	Monitor blood sugar - Adjust dose if needed. Hypersensitivity may occur with Tolbutamide	CYP2C8
	Glyburide	Hypoglycemia, gastric discomfort, nausea/vomiting – monitor blood sugar and adjust dose as needed	CYP2C9
	Gliclazide	Hypoglycemia, abdominal pain, transaminase elevation	CYP2C9

		– monitor blood glucose and adjust dose.	
	Dapagliflozin	Improves glycemic control in Type 2 DM and improves HF management. May cause hypoglycemia, hypotension, rapid weight loss, dehydration, worsen urinary tract infections – monitor blood sugar, adjust dose	CYP1A2
	Empagliflozin	May cause dehydration, hypotension, hypoglycemia and increased urinary tract infection – monitor glucose and body weight and adjust dose	UGT1A9
Other Commonly Used Drugs			
Anti-asthmatic	Formoterol	A long acting B-2 agonist used for the control of asthma. May cause increased bronchospasm – monitor wheezing, adjust dose or change to short-acting product	UGT2B7
	Theophylline	May cause nausea, diarrhea, tachycardia, insomnia – reduce dose or change to other drug. Has lots of DD interactions	CYP1A2
Anti-convulsant	Phenytoin Trimethidione Carbamazepine	***The taking of Phenytoin and Carbamazepine are listed exclusion criteria for this study (Appendix 17.7)*** Assess for excessive adverse effects such as drowsiness, swelling of	CYP2C8

		gums – Adjust dose or substitute other agent	
	Valproic Acid	Nausea and vomiting, drowsiness, dry mouth, transaminase elevations – monitor liver enzymes – adjust dose or change medication	CYP2C9
	Phenobarbital	***The taking of Phenobarbital is a listed exclusion criteria for this study (Appendix 17.7)*** Anti-seizure activity. Drowsiness, confusion – reduce dose or d/c	CYP2C9
Anti-diarrheal	Loperamide	May cause dehydration, weakness, faintness, rapid heart rhythm – discontinue if possible	CYP2C8
Anti-histamine	Loratadine	Can cause sleepiness, dry mouth, allergic reactions - Assess need for this medication during current illness	CYP2C19
Anti-depressant	Amitriptyline	May cause blurred vision, postural hypotension, dry mouth, constipation, urinary retention, suicidal thoughts - Reduce dose if appropriate.	CYP2C19
	Imipramine Nortriptyline	Can cause dry mouth, drowsiness, hypotension, urinary retention and ECG changes – adjust dose or change med	CYP2C19
	Fluoxetine Paroxetine	May cause sleep disorder, sexual dysfunction, mania, suicidal behaviour – adjust dose or change med	CYP2C19

Anti-inflammatory (Non-steroidal)	Diclofenac Ibuprofen Naproxen Celecoxib Ketorolac Meloxicam	If taking long term, there may be abdominal discomfort, pain, nausea and increased risk of bleeding and renal damage - Should be discontinued if concern of toxicity.	CYP2C8
	Valdecoxib	May cause GI bleeding – Discontinue if not required	CYP2C9
Anti-inflammatory (Other)	Chloroquine Hydroxychloroquine	QT prolongation, nausea, vomiting, diarrhea, muscle twitching, Tinnitus/deafness – assess QT, adjust dose or discontinue drug	CYP2C8
	Phenylbutazone	Used mostly in animals recently. Can cause gastric irritation and bleeding and increase action of warfarin anti-coagulants – change to other anti-inflammatory	CYP2C9
	Indomethacin	Can cause edema, increased potassium, sodium, creatinine and hypertension – adjust dose or change medication	CYP2C19
Antipsychotic	Clozapine	May cause low WBC, drowsiness, increased salivation, hypotension, blurred vision, seizures and cardiac inflammation (myocarditis) – monitor WBC, ECG – reduce dose or chose another agent	CYP2C8
	Haloperidol	QT prolongation, tardive dyskinesia – adjust dose or use different medication	CYP2C9

Anti-viral	Remdesivir	Recently approved for use in COVID-19. May cause hypersensitivity reactions and increases in transaminases – slow infusion	CYP2C8
Anti-fibrotic	Pirfenidone	May cause nausea, GERD, skin rash, increased transaminases, dizziness, fatigue, weight loss – adjust dose or d/c during COVID-19 illness.	CYP1A2
Analgesic	acetaminophen	May cause liver damage if blood levels are too high for too long – reduce dose or use another analgesic	CYP1A2
Anxiolytic	Diazepam	May cause drowsiness, poor coordination, suicidal thoughts – reduce dose/change medication	CYP2C8
Sedatives/hypnotics	Zopiclone	Can cause depression, confusion, nightmares and even hallucinations - Dose should be adjusted or d/c if possible	CYP2C8
Cancer Therapeutics	Paclitaxil Cyclophosphamide	Assess for toxic effects such as platelet count - Consult with oncologist	CYP2C8
	Enzalutamide	***The taking of Enzalutamide is a listed exclusion criteria for this study (Appendix 17.7)***	CYP2C8
Hormone	Estradiol	May increase risk of venous thrombosis, heart attack, stroke - Should be discontinued if possible in prothrombotic state of COVID-19	CYP2C8

	Progesterone	Reduce dose	CYP2C9
Estrogen receptor modulator	Tamoxifen	Slight increase in risk of PE, stroke, uterine cancer. Causes hot flashes, weight loss – adjust dose or d/c	CYP2C9
Proton Pump Inhibitor	Pantoprazole	Allergic reactions, c difficile infection – adjust dose or change medication	CYP2C19
	Omeprazole	Nausea & vomiting, abdominal pain, C difficile infection – reduce dose/change medication	CYP2C8
H2 antagonist	Ranitidine	May cause headaches, bradycardia, liver damage, increase c difficile infection – adjust dose or change to other agent	CYP1A2
Serotonin 2C receptor Antagonist	Lorcaserin	Weight loss agent. Removed form USA market in 2020 due to increased cancer risk	CYP2B6
St John's Wort		***The taking of St John's Wort is a listed exclusion criteria for this study (Appendix 17.7)*** May cause sleep disorder, anxiety, fatique, dizziness, headaches – adjust dose or discontinue	CYP2C19

17.11 CMR Protocol

A cardiac magnetic imaging (CMR) examination will be obtained in approximately 150 patients at selected sites although will not be selected on the basis of any specific criteria of their COVID-19 disease. Patients will be asked for consent to participate in this additional assessment at the time of their consent to participate in the study. The CMR study will be performed at the time of the 28-day visit; if this is not possible, the procedure will be arranged for the Day 45 visit. It is anticipated that all such patients will have been discharged from hospital by this time and will be asked to return as outpatients for the procedure.

CMR is well established as an excellent method to assess cardiac structure (including tissue characteristics) and function. It is the prime method to detect cardiac inflammation and is used extensively to diagnose and follow patients with inflammatory heart diseases, as well as the consequences – including, edema, necrosis, scar, regional and global dysfunction, chamber dilatation and heart failure. Importantly, CMR has now been established as a reproducible means to detect and quantitate fibrosis that results from the inflammation. CMR has become the standard for diagnosis of myocarditis in North America using established diagnostic criteria (Lake Louise Criteria for CMR in myocardial Inflammation (1); these criteria have more recently been updated (2).

RATIONALE

There are two rationales for adding CMR to this study:

1. There have been limited reports of CMR findings in patients with COVID-19. In one small study of recovered patients, Huang and colleagues (3) reported that 58% of the patients had abnormalities on CMR, consisting of edema and scarring, with the latter reflected by late gadolinium enhancement. In a more recent report (4) that has received extensive attention, 100 patients who had recovered from COVID-19, had a CMR examination. Two thirds of these patients had mild disease and had recovered at home. However, 33 of the 100 patients had more severe disease and were treated in hospital; 28 received supplemental oxygen and 2 required mechanical ventilation. The time from the onset of illness to the CMR examination ranged from 64 - 92 days. At the time of the CMR, 5 patients had significantly elevated hs-troponin suggestive of ongoing myocyte destruction, whereas another 71 patients had detectable levels of hs-troponin.

   A total of 78 of these patients had abnormal CMR examinations. There was raised myocardial native T1 values (suggestive of edema or scar) in 73 patients and raised myocardial native T2 values in 60 (consistent with inflammation). In addition, approximately one third had myocardial late gadolinium enhancement and 22 had pericardial enhancement. On the day of the examination, some patients had persistent symptoms; atypical chest pain in 17, palpitations in 20, and slightly more than a third complained of ongoing shortness of breath and general exhaustion. Of these patients, 25 had symptoms with less than normal activity, although only 4 had been treated in hospital. This reported prevalence of symptoms and abnormal CMR findings is higher than that in other, albeit, smaller studies. Clearly, there is a need for further investigation to help clarify the extent and nature of ongoing cardiac inflammation in these patients.

2. Importantly, the proposed study will allow us to actually quantify the amount of fibrosis (by measuring the cardiac extracellular volume) in these patients and to compare the active treatment group to those treated with placebo. It would be an important observation if the patients treated with CardiolRx have less fibrosis than the placebo-treated group, offering convincing collaboration of our pre-clinical findings in which CBD significantly reduced myocardial fibrosis in the presence of inflammation.

STATISTICAL ANALYSIS

There will not be a baseline CMR study for comparison. Therefore, the mean values of the parameters of interest (see below) will be compared between the active and the placebo groups after 28 days of treatment with CardiolRx. An added benefit will be the opportunity to compare ultrasound measures of structure and function with the CMR variables in the same patients, and on the same day.

CMR ANALYSES

- Analyses will be performed in a core laboratory using the standardized operating procedures of the CMR Core Lab.

SOFTWARE AND DATA FORMAT

- cvi42 version 5.11 (Circle CV Imaging Inc., Calgary, AB, Canada) will be used for CMR analyses. This software is FDA (CFR 21 part 11) approved, and the software respects all Core lab requirements for the CMR analysis.
- Evaluation contours and quantitative results will be transferred in the format <cvi42 workspace> or as CSV data, respectively.

CMR IMAGE QUALITY ASSESSMENT

Before the evaluation, the submitted scan data will be assessed for completeness (all required images are available and can be evaluated) As well as for image quality. The image quality will be deemed adequate, if the following criteria are fulfilled:

- The cardiac anatomical structures are clearly identifiable.
- The images and the regions of interest (especially the myocardium) are not significantly distorted by field inhomogeneities, motion artifacts, or other artifacts.
- A *Form of Acceptability* will be developed by the core lab in the (RedCap™) MUHC database and will be sent to the site for confirmation that the patient is accepted or refused in the study.

CMR: DIAGNOSTIC TARGETS AND PARAMETERS

1. LV/RV volume
   - LVEDVI, LVESVI
   - RVEDVI, RVESVI
2. LV/RV function
   - LVEF, RVEF
   - Strain: Global longitudinal strain (GLS), segmental GLS (segments 1-12)
   - LV-CI
3. LV mass
   - LV mass index (g/m height), LV mass index (g/m2 BSA)
4. LV edema
   - Global LV myocardial T1
   - Global LV myocardial T2
   - Segmental myocardial T1 (segments 1-12)
   - Segmental myocardial T2 (segments 1-12)
5. LV inflammatory injury
   - Global LV myocardial T1
   - Segmental myocardial T1 (segments 1-12)
   - Global Extracellular Volume (ECV)
   - Regional (>2SD above normal) Extracellular Volume (ECV)

- Presence of necrosis/scar in LGE images [categorical value]

INCIDENTAL FINDINGS

Images will not be assessed for incidental findings. If the reader identifies a clinically significant abnormality beyond the scope of the trial, it will be reported to the Data Safety Monitoring Committee of the trial.

DATA TRANSFER AND STORAGE

1. Images will be transferred via a secured internet transfer protocol. The images will use a Core LAB anonymization tool. This tool will be used in a web browser.
2. The software will anonymize the patient data at the sender hospital and will send the de-identified to the CORE lab. The technical Director of the CMR Core lab will create the Anonymization tool to meet the requirements of the protocol.
3. The transfer will occur via a https secure protocol. The site will have one login and password to be able to use the tool. Once the Images are received at the CORE laboratory, the images will be assessed for acceptability and subsequent analysis.

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