Clinical Study Protocol

Study Title:	**Impact of CARdioIRx™ on MyoCardial Recovery in patients witH AcutE MyocaRditis** A double-blind, placebo-controlled trial (**ARCHER**)
Sponsor:	Cardiol Therapeutics Inc. 2265 Upper Middle Road East Suite 602 Oakville, ON, L6H 0G5, Canada
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Signature Page for Sponsor

Protocol No. Cardiol 100-002

Impact of CardiolRx™ on Myocardial Recovery in Patients with Acute Myocarditis

A double-blind, placebo-controlled trial (ARCHER)

Lead Author:

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Title:	**Impact of CardiolRx™ on Myocardial Recovery in Patients with Acute Myocarditis (ARCHER)**
Product :	**CardiolRx™**
Protocol No.:	**Cardiol 100-002**
Protocol Amendment 2	
Date:	December 19, 2024

I have read this protocol 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	**Impact of CardiolRx™ on Myocardial Recovery in Patients with Acute Myocarditis** A double-blind, placebo-controlled trial (ARCHER)
Diagnosis	Acute Myocarditis
Rationale	Myocarditis is an acute inflammatory condition of the myocardium. Presentation of the disease may be fulminant and necessitate cardiac support, or even result in sudden cardiac death; milder cases are usually self-limiting but may progress to dilated cardiomyopathy with eventual end-stage heart failure. Other than treatments for associated heart failure there are no specific indicated treatments for myocarditis. CardiolRx™ (cannabidiol [CBD] solution), which is known to have anti-inflammatory properties, is being investigated to treat the underlying inflammatory process and thereby favorably modify acute myocarditis. The primary endpoints of the trial are cardiac magnetic resonance (CMR) measures of longitudinal strain (GLS) and myocardial edema (extra cellular volume [ECV]) which have been shown to predict long term prognosis of patients with acute myocarditis.
Inclusion Criteria	1. Males and females 18 years of age or older 2. Diagnosed with acute myocarditis including: a) Clinical criteria (symptoms of chest pain, arrhythmia or shortness of breath, or history of viral-like illness), preferably followed by elevated troponin ***PLUS*** b) CMR diagnosis (Lake Louise Criteria) within 10 days prior to randomization ***OR*** c) Endomyocardial biopsy (EMB) showing either cellular inflammation and/or immunohistochemistry consistent with inflammation. 3. Male subjects with partners of childbearing potential who have had a vasectomy or are willing to use double barrier contraception methods during the conduct of the study and for 2 months after the last dose of study drug. 4. Women of childbearing potential willing to use an acceptable method of contraception starting with study drug administration and for a minimum of 2 months after study completion. Otherwise, women must be postmenopausal.
Key Exclusion Criteria	1. Coronary artery disease (CAD) defined as a stenosis greater than 50% in a major epicardial coronary artery 2. Severe valvular heart disease 3. Inability to safely undergo CMR including administration of gadolinium

	4. Estimated glomerular filtration rate (eGFR) < 30 ml/min 5. 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. 6. Sepsis, defined as documented bacteremia at the time of presentation or other documented active infection. 7. Severe left ventricular (LV) dysfunction - requiring inotropic support, left ventricular assist device (LVAD) or other circulatory assist devices, or urgent need for transplantation 8. Documented biopsy evidence of giant cell or eosinophilic myocarditis 9. Prior history of sustained ventricular arrhythmia
Primary and Secondary Efficacy Objective	To evaluate the effect of CardiolRx™ on myocardial recovery in patients presenting with acute myocarditis
Primary Efficacy Outcome	The primary outcome of this study is comprised of two primary endpoints, i.e., the difference in the means of each: ECV, and GLS, as measured by CMR at 12 weeks post randomization between the active and the placebo groups.
Secondary Efficacy Outcome	The secondary outcome of this study is the difference in the means of left-ventricular ejection fraction (LVEF), as measured by CMR at 12 weeks post randomization between the active and the placebo groups.
Other Efficacy Outcomes	- Survival, free from major event (cardiac transplant, left-ventricular assist device (LVAD), hospitalization for heart failure (HF)) through 12 weeks post randomization - Change in CMR parameters from baseline to 12 weeks post randomization: LVEF, ECV, GLS, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left atrial end-systolic volume (LAESV), LV mass, late gadolinium enhancement (LGE) imaging, degree of edema - Change in New York Heart Association (NYHA) classification at 12 weeks post randomization from baseline - Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) from baseline to 12 weeks post randomization - Time to resolution of clinical symptoms, including chest pain, arrhythmias, shortness of breath - Time to normalization of high sensitivity troponin (hs-troponin), N-terminal pro B-type naturetic peptide (NT-proBNP) and inflammatory markers: high sensitivity C reactive protein (hs-CRP), ferritin, tumour necrosis factor alpha (TNF-alpha), interleukin 1-beta (IL-1 beta), interleukin 6 (IL-6), interleukin 10 (IL-10), interleukin 18 (IL-18) and endothelial markers: soluble vascular cell adhesion molecule-1

	(sVCAM-1), transforming growth factor beta (TGF-beta [beta 1 and beta 2]) - Change in hs-troponin, NT-proBNP and inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2]) from baseline to week 12 - Time to normalization of electrocardiogram (ECG) abnormalities
Safety Objective	The primary safety objective is to demonstrate that administration of CardiolRx™ in the proposed doses in this patient population is safe.
Safety Parameters	Safety parameters include the number of adverse events (AEs) and serious adverse events (SAEs), changes in ECG parameters, Columbia Suicide Severity Rating Scale (C-SSRS) as well as changes in laboratory parameters, including liver function parameters and International Normalized Ratio (INR) during the 13-week study period.
Additional Assessments:	Serum plasma will be retained for measurement of CBD drug levels (as indicated in Section 4.3) as well as for hs-troponin, NT-proBNP, inflammatory markers and endothelial markers (as indicated in Section 4.1.3) at defined time points (as indicated in Section 17.2).
Number of Patients/Sites:	100 patients will be randomized (50 to CardiolRx™ and 50 to placebo) at centers in Canada, the United States, Israel, Brazil and Europe.
Scheduled Duration of Study:	Estimated 15 months recruitment, 13 weeks follow-up, 3 months data cleaning and 3 months statistical analysis and reporting. If all timelines are met, the total duration of the study will be approximately 24 months.
Design & Methodology	Multi-center, double-blind, randomized, placebo-controlled, parallel group design. 1:1 randomization; treatment will be stratified within sites. Patients diagnosed with acute myocarditis by an EMB or a CMR will be screened within 10 days of the diagnostic CMR. Informed consent will be obtained at this point. For patients who have been diagnosed using an EMB, a CMR needs to be performed as well, which will be included in the informed consent form (ICF). Eligible patients will then be randomized within 10 days from the CMR assessment. Baseline assessments include the following: Clinical assessment, including vital signs, ECG; Hematology and blood chemistry, NYHA classification, C-SSRS and KCCQ. Frozen plasma will be retained for central analysis of CBD, hs-troponin, NT-proBNP and inflammatory markers. Study treatment needs to be taken with food and will be initiated in the evening of Day 1, after all baseline assessments have been completed and the patient has been randomized. Oral administration is as follows: • Week 1 (p.m. dose of Day 1 to a.m. dose of Day 7): 2.5 mg/kg of body weight b.i.d. CardiolRx™ or placebo

	• Week 2 (p.m. dose of Day 7 to a.m. dose of Day 14): 5 mg/kg of body weight b.i.d. CardiolRx™ or placebo • Week 3 (p.m. dose of Day 14 to a.m. dose of Day 21): 7.5 mg/kg of body weight b.i.d. CardiolRx™ or placebo • Week 4 to end of treatment period (p.m. dose of Day 21 to a.m. dose of last day of treatment period at week 12): 10 mg/kg of body weight b.i.d. CardiolRx™ or placebo • The morning and evening doses should be taken within an 6 – 18-hour window of each other If the next higher dose after each study drug increase is not tolerated, the dose will be reduced to the previous tolerated dose. Every visit (before the next dose increase) the patient will be re-evaluated. This includes intensive ECG monitoring at approximately 5 hours post-morning dose (time of maximum concentration [T_{max}]) to surveil for deleterious effects on ECG intervals (particularly the QTc interval) and rhythm. Drug titration will be dependent on investigator or designate interrogation of the ECGs and the absence of abnormalities on those ECGs. Vital signs, concurrent medication and AEs, including SAEs will be recorded, blood chemistry including liver function tests, hematology as well as INR assessments will be carried out. Final efficacy assessments (including a second CMR) will take place after 12 weeks of study treatment. A final safety assessment will take place after 13 weeks, 1 week after completion of study treatment.
Concomitant Treatments	Patients may be treated with corticosteroids and may be on the standard of care treatment for HF as prescribed by their treating physician, including angiotensin receptor blockers (ARBs)/ angiotensin-converting enzyme inhibitors (ACE-inhibitors), diuretics, and beta-blockers. They should not be taking any cannabinoids, digoxin, type 1 or 3 antiarrhythmics, or strong inducers of CYP3A4 and CYP2C19 (see Appendix 17.8). Drugs that are known to prolong QTc intervals must not be started during the study (Appendix 17.10).
Data Safety and Monitoring	A Data Safety and Monitoring Committee (DSMC) will review all safety events on an ongoing ad hoc basis by treatment code and will make recommendations to the Steering Committee on further conduct of the study.
Statistical Analysis Approach	*Primary and secondary efficacy analyses:* For each of the two primary endpoints and the secondary endpoiont, the means at 12 weeks will be compared between the active and the placebo groups, applying an analysis of covariance (ANCOVA), adjusted for baseline means. The obtained two primary outcome p-values will be considered statistically significant following the Hochberg Procedure.(Benjamini and Hochberg 1995) The primary analysis will follow the intention-to-treat principle. A per-protocol secondary analysis may be considered.

	Other efficacy analyses: Descriptive statistics will be used to compare baseline characteristics between the two groups. Continuous variables will be expressed as mean ± standard deviation (SD), categorical variables will be expressed in counts with percentages. The differences in CMR parameters and other continuous secondary outcomes from baseline to 12 weeks post randomization between the two treatment groups will be analyzed using an ANCOVA analysis. Treatment effect estimates and 95% confidence intervals will be determined. The changes in hs-troponin, in NT-proBNP, in inflammatory markers and in endothelial markers from baseline to 12 weeks will be analyzed applying an area-under-the-curve (AUC) analysis using all available time points. Binary outcomes will be compared using a chi-square test. The differences in proportions experiencing these outcomes will be estimated, along with 95% confidence intervals. *Safety analyses:* The difference in continuous outcomes will be analyzed as described above. For dichotomous safety outcomes, the difference in proportions experiencing these will be estimated, with 95% confidence intervals.

2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
ALT	Alanine Aminotransferase
a.m.	Morning
ANCOVA	Analysis of Covariance
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BBB	Bundle Branch Block
b.i.d.	Twice a Day
BNP	Brain Natriuretic Peptide
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CBD	Cannabidiol
CMR	Cardiac Magnetic Resonance Imaging
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computed Tomography
CV	Cardiovascular
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DM	Diabetes Mellitus
DOX	Doxorubicin
DSMC	Data Safety and Monitoring Committee
EAM	Experimental Autoimmune Myocarditis

Abbreviation	Definition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECV	Extracellular Volume
eDCF	Electronic Data Clarification Form
EDV	End Diastolic Volume
eGFR	Estimated Glomerular Filtration Rate
EMB	Endomyocardial biopsy
ESV	End Systolic Volume
FDA	Food and Drug Administration
GBD	Global Burden of Disease
GCP	Good Clinical Practices
GLS	Global longitudinal strain
GPR	G-Protein-coupled Receptor
HF	Heart Failure
HR	Heart Rate
hs-CRP	High Sensitivity C Reactive Protein
hs-troponin	High Sensitivity Troponin
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFN-gamma	Interferon-gamma
IL-1 beta	Interleukin 1-beta
IL-6	Interleukin 6
IL-10	Interleukin 10
IL-18	Interleukin 18
INR	International Normalized Ratio
IRB/REB	Institutional Review Board/Research Ethics Board

Abbreviation	Definition
ITT	Intention-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAESV	Left Atrial End-Systolic Volume
LBBB	Left Bundle Branch Block
LGE	Late gadolinium enhancement
LV	Left ventricular
LVAD	Left ventricular assist device
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LAESV	Left atrial end-systolic volume
LVESV	Left ventricular end-systolic volume
MCP1	Monocyte Chemoattractant Protein-1
MCT	Medium-chain triglyceride
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
p.m.	Afternoon
PPAR-gamma	Peroxisome Proliferator-Activated Receptor Gamma
RBBB	Right Bundle Branch Block
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	Standard of Care
sVCAM-1	Soluble Vascular Cell Adhesion Molecule-1
TGF-beta	Transforming Growth Factor Beta
THC	Tetrahydrocannabinol
T_{max}	Time to Maximum Concentration
TNF-alpha	Tumour Necrosis Factor Alpha

Abbreviation	Definition
TRP	Transient Receptor Potential
ULN	Upper Limit of Normal

3 BACKGROUND

3.1 Description of Acute Myocarditis

Acute Myocarditis is an uncommon condition characterized by inflammation of the heart tissue which may result in chest pain, impaired cardiac function, atrial and ventricular arrhythmias and conduction disturbances. The presentation may be fulminant and necessitate cardiac support, or even result in sudden cardiac death; milder cases are usually self-limiting but may progress to dilated cardiomyopathy with eventual end-stage heart failure.

Although the etiology of acute myocarditis is very varied, the most common cause in the developed world is viral infection in the myocardium.(Sagar, Liu, and Cooper 2012)·(Trachtenberg and Hare 2017) Common viruses associated with myocarditis include adenovirus, enterovirus, parvovirus B19, herpes virus, Epstein-Barr virus and cytomegalovirus.(Dominguez et al. 2016) Influenza A and B have also been associated with myocarditis although the prevalence seems low.(Sellers et al. 2017) Clinically diagnosed myocarditis in hospitalized patients with documented influenza infection has been reported in 0.4 to 13% of cases.(Kodama 2010; Karjalainen, Nieminen, and Heikkilä 1980) Other viruses that uncommonly cause myocarditis include hepatitis C (Matsumori et al. 2002) and human immunodeficiency virus.(Kindermann et al. 2012)

In addition to viruses, myocarditis can be triggered by other infectious processes such as Chagas disease, Lyme disease and even diphtheria.(Sagar, Liu, and Cooper 2012; Kindermann et al. 2012) Myocarditis can also be precipitated by a large number of chemical entities; examples include certain chemotherapeutic agents such as anthracylines,(Volkova and Russell 2011) trastuzumab (Herceptin) (Suter, Cook-Bruns, and Barton 2004) and the more recently introduced checkpoint inhibitors.(Mahmood et al. 2018) Some antipsychotic agents such as clozapine can also induce inflammation in the myocardium.(Kilian et al. 1999)

Finally, myocarditis has also been reported in association with a number of clinical syndromes, including reactions to certain drugs (such as penicillin), systemic autoimmune disease such as Churg-Strauss (Vinit 2010), Loeffler's disease (Corssmit, Trip, and Durrer 1999) and an eosinophilic infiltration post smallpox vaccination.(Murphy et al. 2003)

The exact pathophysiology of myocarditis is not completely understood. In viral infection-mediated myocarditis, viral proliferation in myocytes can cause direct tissue injury. However, most tissue damage in myocarditis results from the interaction of the viral trigger with the immune system. The immune response is activated to eliminate as many virus-infected cells as possible to control the infection, but this response needs to be modulated and turned off when appropriate; otherwise, there will be excessive inflammatory tissue damage. Viral persistence can expose the host to a prolonged

antigenic trigger, chronic immune activation, and the potential for chronic myocarditis. Intracellular components released from necrotic myocytes may trigger an autoimmune response by molecular mimicry with viral antigens.(Sagar, Liu, and Cooper 2012) It is the autoimmune response that results in continued cell necrosis, development of fibrosis, and further impairment in cardiac function; and, is believed to lead to the development of chronic dilated cardiomyopathy. Dilated cardiomyopathy remains the leading reason for cardiac transplantation.(Fung et al. 2016; Maron et al. 2006) It is acute viral myocarditis with ongoing inflammatory damage to the myocardium that is the focus of this study.

3.2 Prevalence

A Global Burden of Disease (GBD) report published in 2015 reported myocarditis prevalence data from 1990 to 2013 collected worldwide. The number of cases increased from approximately 960,000 (1990) to 1,480,000 (2013) (GBD Study 2013). Prevalence between this time span remained stable at about 22 per 100,000.(Forouzanfar et al. 2016)

GBD study results published in 2018 suggested a global prevalence of myocarditis of 1,804,600 as of 2017 (prevalence of approximately 24 in 100,000).(James et al. 2018) Given the dearth of data for the US population, stability of global prevalence of less than 25 per 100,000 from 1993 to date, and difficulty in diagnosing this disease, generalization of global data seems to offer a reasonable option to posit acute myocarditis prevalence of 24 (approx.) per 100,000 in the US. Such a generalization is further supported by a lack of evidence linking myocarditis with a region or race predilection. Although country/region-specific prevalence of microbial infections could potentially impact the extent of generalization, such claims are not accompanied by analyses or substantive citation of sources.

3.3 Clinical Course

The clinical course of acute myocarditis is quite variable and extends from the asymptomatic and often undetected cases through to fulminant disease which has a significant acute mortality.(Sagar, Liu, and Cooper 2012; Dennert, Crijns, and Heymans 2008) The presentation is classically a young adult (males > females) complaining of shortness of breath with precedent (days to weeks) symptoms of an acute viral (either respiratory or gastro-intestinal) illness. Examination may reveal signs of heart failure, occasionally accompanied by a pericardial rub consistent with acute pericarditis. The electrocardiogram is usually abnormal with non-specific ST-T abnormalities, evidence of conduction system disease or findings suggestive of acute pericarditis. Both atrial and ventricular rhythm abnormalities are frequent. In some cases, sudden unexpected death occurs early in the course of the disease. Echocardiography usually reveals evidence of left ventricular dysfunction (often with a normal sized chamber early on) with or without pericardial effusion. Later on, the ventricles may dilate.

On occasion, the presentation is more dramatic with chest pain and electrocardiographic findings of elevated ST segments suggestive of myocardial infarction. The distinction is sometimes difficult and such patients may require coronary angiography to exclude epicardial coronary occlusion as the cause of presentation. In a small portion of patients, the presentation is that of fulminant heart failure; these patients usually require intensive care with mechanical cardiac assist. Although mortality is significant in these patients, many do recover. Indeed, it was believed that if such patients survived the acute event, then the prognosis was excellent with full recovery (Dennert, Crijns, and Heymans 2008; McCarthy et al. 2000), with a better long-term prognosis than those without the fulminant presentation. However, subsequent studies have not supported this observation.(D'Ambrosio et al. 2001; Ammirati et al. 2017) In the study by Ammirati et al (Ammirati et al. 2017), the in-hospital mortality rate or need for transplantation was 25.5% in 55 patients who needed inotropes or mechanical circulatory assist compared to 0% in the 132 non-fulminant group. At 9 years, the transplant-free survival was significantly greater in the non-fulminant group (100%) than in those with a fulminant presentation (64.5%).

3.4 Current Treatment Options

There is no specific treatment for acute myocarditis. However, it is generally agreed that all patients with acute myocarditis should receive guideline-indicated medical treatment for heart failure as indicated by the clinical presentation (Tschöpe et al. 2019). This includes ACE inhibitors and/or ARBs, beta blockers, diuretics and aldosterone inhibitors. In addition, if arrhythmias or conduction system abnormalities are present, guideline-supported approaches for these issues should be used. If the presentation is one of fulminant heart failure, then inotropic support and possibly mechanical circulatory support or veno-arterial extracorporeal life support are indicated.(Ammirati et al. 2017) Obviously, these patients require an intensive care environment until they stabilize and ventricular function improves. There is a high mortality during this period.(Ammirati et al. 2017) Others in this group will respond to intensive therapy and stabilize on chronic therapy for heart failure. Some of these, and others with a non-fulminant presentation will progress to chronic dilated cardiomyopathy with chronic progressive heart failure.

Many other therapies have been trialed for acute myocarditis. For those with acute viral myocarditis, it is believed that the intense inflammation in the myocardium helps to eliminate the virus quickly and thereby avoids more extensive tissue damage. In some patients, the inflammation persists despite viral elimination – possibly due to an autoimmune process. It is for these patients that the search goes on for more effective therapy. There has been evidence in these virus negative patients with persistent LV dysfunction, that immunosuppressive therapy is beneficial.(Frustaci, Russo, and Chimenti 2009) In the study by Frustaci and colleagues, after at least 24 weeks of conventional therapy, patients were randomized to either placebo or cortisone and azathioprine.(Frustaci, Russo, and Chimenti 2009) The LVEF improved in almost 90% of the treated group versus none in the placebo group. In another study with long term follow-up (100 months), the authors also found that immunosuppressive therapy was

associated with better heart transplant-free survival.(Merken et al. 2018) Unfortunately other studies have not reported these positive findings.(Mason et al. 1995)

Some therapies have been aimed at eliminating the virus. Since enterovirus and adenoviruses directly infect the cardiomyocytes, viral clearance with a 6-month course of Interferon beta was associated with an improvement in LVEF in a non-randomized study.(Kühl et al. 2003) Those with viral clearance had a better survival than those with viral persistence.(Kühl et al. 2012) Unfortunately, to date, randomized trials have not established anti-viral therapy as efficacious for acute myocarditis.(Tschöpe et al. 2019)

Other approaches that have not proven efficacious include intra-venous immunoglobulin (McNamara et al. 2001); however, this may be effective for certain viral subtypes. (Maisch et al. 2004) Colchicine, a plant alkaloid has become the preferred treatment for acute pericarditis (Imazio et al. 2013) but as yet, has not been demonstrated to improve outcomes in acute myocarditis, at least when myocardial necrosis is also present. Other immune-suppressive and immune-modulatory approaches are being tested.(Tschöpe et al. 2019) One such approach is the use of anakinra, an interleukin-1 receptor antagonist (Fleischmann, Stern, and Iqbal 2004) which is administered subcutaneously to help manage rheumatoid arthritis. This approach has been reported to be beneficial in the management of patients with acute fulminant myocarditis with severe heart failure.(Cavalli et al. 2016) However, there are currently no data about the efficacy of anakinra for acute myocarditis without fulminant heart failure.

In summary, whereas all patients with a diagnosis of acute myocarditis should be monitored carefully during the acute phase of the illness and managed with guideline directed therapies for heart failure, arrhythmia and conduction disturbances, there is no uniformly recommended therapy for the underlying inflammatory process.

3.5 Rationale

It is proposed that CardiolRx™ (cannabidiol (CBD) solution), can treat the underlying inflammatory process and thereby favorably modify acute myocarditis, based upon the known anti-inflammatory properties of CBD.

CBD improves endothelial function, and endothelial dysfunction is an important therapeutic target in a number of cardiovascular (CV) diseases including heart failure. CBD reduces inflammatory activation of the endothelial lining of blood vessels(Rajesh et al. 2007) thus improving endothelial vaso-relaxation (Saoirse E. O'Sullivan et al. 2009; Stanley et al. 2015) and blood flow. 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 CV disease patients. CBD has also been shown to be protective against doxorubicin (DOX)-induced cardiotoxicity, including reducing pro-inflammatory responses in the heart.(Fouad et al. 2013; Hao et al. 2015)

A murine model of experimental autoimmune myocarditis (EAM) 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 (IL-6, IL-1 beta, Interferon-gamma [IFN-gamma], Monocyte Chemoattractant Protein-1 [MCP1]), reduced markers of oxidative stress and reduced myocardial fibrosis.(Lee et al. 2016)

The effect of CBD was also investigated on the cardiomyocyte cell line H9c2. H9c2 cells respond to angiotensin II by increasing in size, reflecting the myocardial hypertrophy seen in heart failure. The surface area of cultured cardiomyocytes is significantly increased by angiotensin II, and this increase is significantly decreased by CBD. Similarly, the expression of both Brain Natriuretic Peptide (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, the animal model of heart failure in male C57BL/6 mice, based on the published method of Cordero-Reyes has been used to assess CBD effectiveness.(Cordero-Reyes et al. 2016) Although not strictly a model of myocarditis, it is a model of cardiac inflammation with associated depression of myocardial function. The results show that CBD reduced inflammation and fibrosis induced by angiotensin-II in this model of heart failure. 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 heart failure, showed that CBD reduced expression of BNP in heart failure hearts (Cardiol Therapeutics, unpublished data). In conclusion, CBD administered by subcutaneous injection reduced a number of markers reflecting heart failure in this model system.

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 (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 GPR55, GPR18, GPR6 and GPR3 (Brown 2007; Laun and Song 2017; Morales and Reggio 2017), although probably not at the canonical endocannabinoid receptors CB1 (Reggio et al. 1995; Mukhopadhyay et al.

2011; McPartland et al. 2017) and CB2.(Mukhopadhyay et al. 2011; McPartland et al. 2017)

In summary, a number of peer-reviewed studies have demonstrated that CBD has anti-inflammatory activity *in vivo* in a range of animal models of both non-CV disorders and CV disease, including in a murine model of experimental autoimmune myocarditis and in *in vitro* and *in vivo* models of heart failure which are associated with myocardial inflammation and fibrosis. Furthermore, there is evidence of binding of CBD to a range of different receptors, a number of which are associated with anti-inflammatory activities which provides a rationale for the application of CBD as a therapeutic approach to the treatment of acute myocarditis.

3.6 Rationale for Primary Endpoint Selection

Changes in LVEF have been traditionally used to assess efficacy of potential therapeutic agents in patients with myocarditis.(Frustaci, Russo, and Chimenti 2009; Kühl et al. 2012; Mason et al. 1995; McNamara et al. 2001; Cavalli et al. 2016) It is readily available by echocardiography although contrast angiography, CMR imaging, computed tomography or radionuclide techniques all give reasonably comparable results.

There are several limitations with this approach.(Cikes and Solomon 2016) First, LVEF does not describe the function of the muscle but rather the change in LV volume over the cardiac cycle. The geometric assumptions used to calculate the end-diastolic and end-systolic volumes are considerable – particularly in patients with segmental wall motion abnormalities. LVEF is also load dependent and values can change considerably with changes in preload or afterload and is only moderately reproducible. In some patients with myocarditis the LVEF is markedly depressed and intensive therapy is required to support the circulation. However, in many (perhaps the majority), the LVEF is within the normal range throughout the course of the acute presentation, with the significance of LVEF changes within the normal range being questionable.(André et al. 2016) Because of these limitations, LVEF was selected as the secondary outcome and not one of the primary outcomes.

More recently, there has been renewed interest in estimating LV strain – perhaps as a more sensitive measure of LV function. The development of speckle tracking by echocardiography provided a reproducible means to measure longitudinal, circumferential and radial strain.(Hsiao et al. 2013) The same measures are available from CMR by images. These studies have revealed that patients presenting with acute myocarditis with normal LVEF measures, have abnormal measures of strain – with longitudinal strain being the most reproducible. Strain measures are also reported to have excellent intra- and inter-observer reproducibility as well as good inter-study agreement (Taylor et al. 2015; Andre et al. 2015) For these reasons, we have decided

to select LV GLS as a primary endpoint to enhance our ability to detect changes in myocardial function in response to therapy with CardiolRx™.

In addition to impairment of LV function, other characteristic features of acute myocarditis are edema (secondary to the inflammation) in the early phases of the disease, followed by necrosis and increased fibrosis in the later phases. Both of these processes expand the extracellular volume in the heart. CMR has been shown to have utility in measuring the ECV in patients with cardiac disease, and is particularly helpful in detecting infiltrative diseases, such as amyloidosis or those with increased fibrosis. In patients with acute myocarditis, CMR measures of ECV have revealed more extensive cellular damage than suspected based solely on assessment of the extent of late gadolinium enhancement (LGE).(Radunski et al. 2017) We have added ECV as a second primary endpoint to GLS in our attempt to better quantify the abnormal function and structure of the myocardium in this disease.

In summary, the primary outcome will consist of two primary endpoints; GLS and ECV – each measured by CMR at baseline and after 12 weeks of therapy. For each of the two primary outcomes, the means at 12 weeks will be compared between the active and the placebo groups, applying an ANCOVA procedure, adjusted for baseline values. The obtained two primary outcome p-values will be considered statistically significant following the Hochberg Procedure.(Benjamini and Hochberg 1995)

4 STUDY OBJECTIVES

4.1 Efficacy

4.1.1 Primary and Secondary Objectives

The primary and secondary objectives are to evaluate the effect of treatment with CardiolRx™ on myocardial recovery for patients presenting with acute myocarditis.

4.1.2 Primary Efficacy Outcome

The primary efficacy outcome of this study is comprised of two endpoints, i.e., the difference in the means of each: extracellular volume (ECV), and global longitudinal strain (GLS), as measured by CMR at 12 weeks post randomization between the active and the placebo groups.

4.1.3 Secondary Efficacy Outcome

The secondary efficacy outcome is the difference in the means in LVEF, as measured by CMR at 12 weeks post randomization between the active and the placebo groups.

4.1.4 Other Efficacy Objectives

Other objectives include the improvement in other clinical parameters from baseline.

4.1.5 Other Efficacy Outcomes

- Survival, free from major event: cardiac transplant, LVAD, hospitalization for HF 12 weeks post randomization
- Change in CMR parameters from baseline to 12 weeks post randomization: LVEF, ECV, GLS, LVEDV, LVESV, LAESV, LV mass, LGE, degree of edema
- Change in NYHA classification from baseline to 12 weeks post randomization
- Change in KCCQ from baseline to 12 weeks post randomization
- Time to resolution of clinical symptoms, including chest pain, arrhythmias, shortness of breath
- Time to normalization of hs-troponin, NT-proBNP and inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2])
- Change in hs-troponin, NT-proBNP and inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2]) from baseline to week 12
- Time to normalization of ECG abnormalities

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 Safety Parameters

Safety parameters include the number of AEs and SAEs, changes in ECG parameters, C-SSRS as well as changes in laboratory parameters, including liver function parameters, and INR during the 13-week study period.

4.3 Study Drug Levels

CBD levels will be measured at baseline, and at 3, 6, and 12 weeks post randomization.

5 STUDY POPULATION

5.1 Enrolment and Study Centers

100 patients (50 on active study medication, 50 on placebo) will be enrolled in centers in Canada, the United States, Brazil, Israel and in Europe.

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. Diagnosed with acute myocarditis including:

    a. Clinical criteria (symptoms of chest pain, arrhythmia or shortness of breath, or history of viral-like illness), preferably followed by elevated troponin ***PLUS***
    b. CMR diagnosis: (Lake Louise Criteria, Appendix 17.4 of this protocol) within10 days prior to randomization ***OR***
    c. Endomyocardial biopsy showing either cellular inflammation and/or immunohistochemistry consistent with inflammation

3. Male subjects with partners of childbearing potential who have had a vasectomy or are willing to use double barrier contraception methods during the conduct of the study and for 2 months after the last dose of study drug.

4. Women of childbearing potential willing to use an acceptable method of contraception starting with study drug administration and for a minimum of 2 months after study completion. Otherwise, women must be postmenopausal (at least 1 y absence of vaginal bleeding or spotting and confirmed by follicle stimulating hormone [FSH] ≥40 mIU/mL [or ≥ 40 IU/L] if less than 2 y postmenopausal) or be surgically sterile. The following reliable methods of contraception are: parenteral contraceptives, oral contraceptives, patch contraceptives, implantable hormonal contraceptives, intrauterine device or system, surgical sterilization (hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy), tubal ligation/occlusion, vasectomized partner, or sexual abstinence, if this is the subject's current practice. Periodic abstinence, i.e., calendar, symptothermal, or post-ovulation methods are not an acceptable form of contraception for this study. These methods of contraception also apply to female partners of male subjects.

*thorough evaluation of ischemia by coronary angiography, computed tomography (CT) angiography and/or stress test; imaging is at the discretion of the principal investigator.

However, for patients < 35 years of age, in the absence of significant risk factors, coronary angiography is discouraged.

5.3 Exclusion Criteria

None of the following criteria can be present to enroll a patient into this study:

1. Coronary artery disease (CAD) defined as a stenosis greater than 50% in a major epicardial coronary artery
2. Severe valvular heart disease
3. Inability to safely undergo CMR including administration of gadolinium
4. Estimated glomerular filtration rate (eGFR) < 30 ml/min
5. 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.
6. Sepsis, defined as documented bacteremia at the time of presentation or other documented active infection.
7. Severe left ventricular (LV) dysfunction requiring inotropic support, left ventricular assist device (LVAD) or other circulatory assist devices, or urgent need for transplantation
8. Documented biopsy evidence of giant cell or eosinophilic myocarditis
9. Prior history of sustained ventricular arrhythmia
10. Acute coronary syndrome within 30 days
11. Percutaneous coronary intervention within 30 days
12. History of QT interval prolongation or QTc interval > 500 msec
13. Treated with strong inducers CYP3A4 or CYP2C19, as listed in Appendix 17.8
14. Treated with digoxin and/or type 1 or 3 antiarrhythmics
15. Current participation in any research study involving investigational drugs or devices
16. Inability or unwillingness to give informed consent
17. Ongoing drug or alcohol abuse
18. Women who are pregnant or breastfeeding
19. Current diagnosis of cancer, with the exception of non-melanoma skin cancer
20. Any factor, which would make it unlikely that the patient can comply with the study procedures
21. On any cannabinoid during the past month
22. Body weight > 170 kg
23. Showing suicidal tendency as per the C-SSRS, administered at screening

6 STUDY DESIGN

6.1 Summary of Study Design

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

Patients diagnosed with acute myocarditis by an EMB or a CMR will be screened within 10 days of the diagnostic CMR. Informed consent will be obtained at this point. For patients who have been diagnosed using an EMB, a CMR needs to be performed as well (which will be included in the ICF) to obtain baseline values of outcome parameters.

Baseline assessments include the following: Clinical assessment, including vital signs and 12-lead ECG; hematology and blood chemistry, NYHA classification, C-SSRS and KCCQ. Frozen plasma will be retained for central analysis of CBD levels as well as hs-troponin, NT-proBNP, inflammatory markers and endothelial markers.

Eligible patients will be randomized within 10 days from the CMR assessment, either to CardiolRx™ or placebo in a 1:1 ratio.

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

Oral administration is as follows:

- Week 1 (p.m. dose of Day 1 to a.m. dose of Day 7):
  2.5 mg/kg of body weight CardiolRx™ b.i.d. or placebo
- Week 2 (p.m. dose of Day 7 to a.m. dose of Day 14):
  5.0 mg/kg of body weight CardiolRx™ b.i.d. or placebo
- Week 3 (p.m. dose of Day 14 to a.m. dose of Day 21):
  7.5 mg/kg of body weight CardiolRx™ b.i.d. or placebo
- Week 4 end of treatment period (p.m. dose of Day 21 to a.m. dose of last day of treatment period at week 12): 10.0 mg/kg of body weight CardiolRx™ b.i.d. or placebo
- The morning and evening doses should be taken within an 6 – 18-hour window of each other

If the next higher dose after each study drug increase is not tolerated, the dose will be reduced to the previous tolerated dose.

6.2 Follow-up Procedures

Every visit (before the next dose increase) the patient will be re-evaluated. This includes intensive ECG monitoring at approximately 5 hours post-morning dose (T_{max}) to surveil for deleterious effects on ECG intervals (particularly the QTc interval) and rhythm.

Drug titration will be dependent on investigator or designate interrogation of the ECGs and the absence of abnormalities on those ECGs.

Vital signs, concurrent medication and AEs, including SAEs will be recorded, blood chemistry including liver function tests, hematology as well as INR assessments will be carried out.

Final efficacy assessments will take place after 12 weeks of study treatment and include a second CMR, a clinical assessment, vital signs, a 12-lead ECG, the KCCQ, the C-SSRS, a NYHA classification as well as laboratory assessments. Frozen plasma will be retained for central analysis of CBD levels as well as hs-troponin, NT-proBNP, inflammatory markers and endothelial markers.

A final safety assessment will take place after 13 weeks, 1 week after completion of study treatment.

6.3 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.

6.4 Study Medication

6.4.1 Active Study Medication

CardiolRx™ (cannabidiol) solution 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	Antioxidant	10 mg/ml	1.0% w/v
Medium Chain Triglycerides	Solvent	0.890 ml	89.0% w/v
Total		1 ml	100.0%

6.4.2 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	Antioxidant	10 mg/ml	1.0 % w/v
Medium Chain Triglycerides	Solvent	q.s. to 1 ml	~99%
	Total	1 ml	100%

6.5 Blinding

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

6.6 Premature Interruption or Withdrawal from Study Treatment

Before a decision is taken on premature discontinuation of study treatment, the medical monitor should be contacted.

6.6.1 Permanent Suspension of Study Treatment

Permanent suspension of study treatment must occur in the following cases:

- 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 9.2.13.3.
- Development of an AE or any medical condition, which, in the opinion of the investigator, necessitates permanent suspension of study treatment.
- Withdrawal of consent.

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 SAEs should be reported, regardless of whether or not the event is of CV origin or occurs under the care of another physician or institution.

6.6.2 Temporary Suspension of Treatment

Temporary suspension of study treatment (up to 7 days) can occur in case of a development of an (S)AE or a medical condition, which, in the opinion of the investigator, necessitates temporary interruption of study treatment.

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.

6.6.3 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.

6.7 Concomitant Treatment

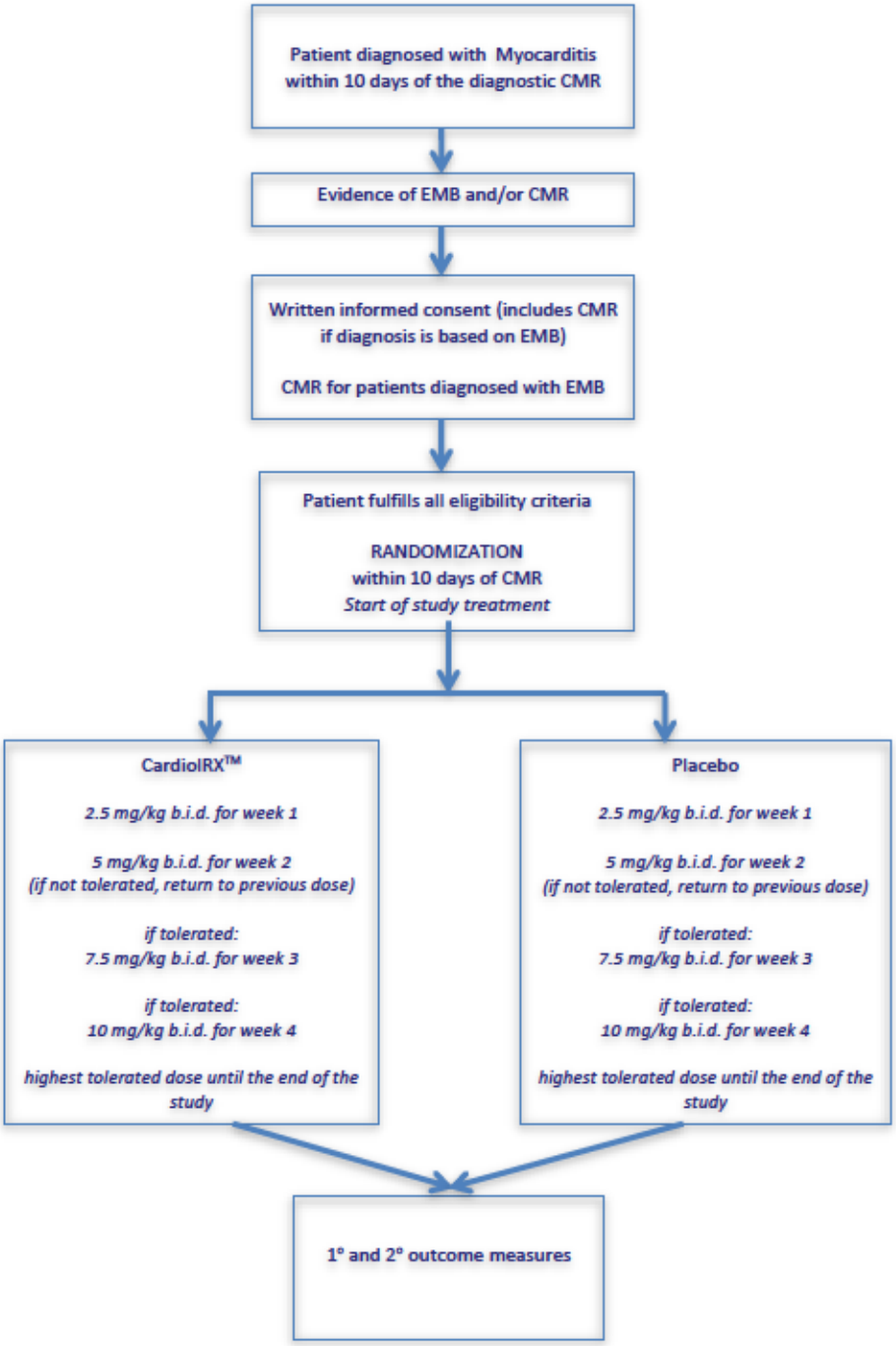
Standard of care (SOC) concurrent medications will not be altered for the purpose of the study. They may include corticosteroids, beta-blockers, ACE-inhibitors, ARBs, and diuretics.

Patients are not allowed to take any cannabinoids, digoxin, type 1 or 3 antiarrhythmics during the study period nor strong inducers of CYP3A4 and CYP2C19 (see Appendix 17.8).

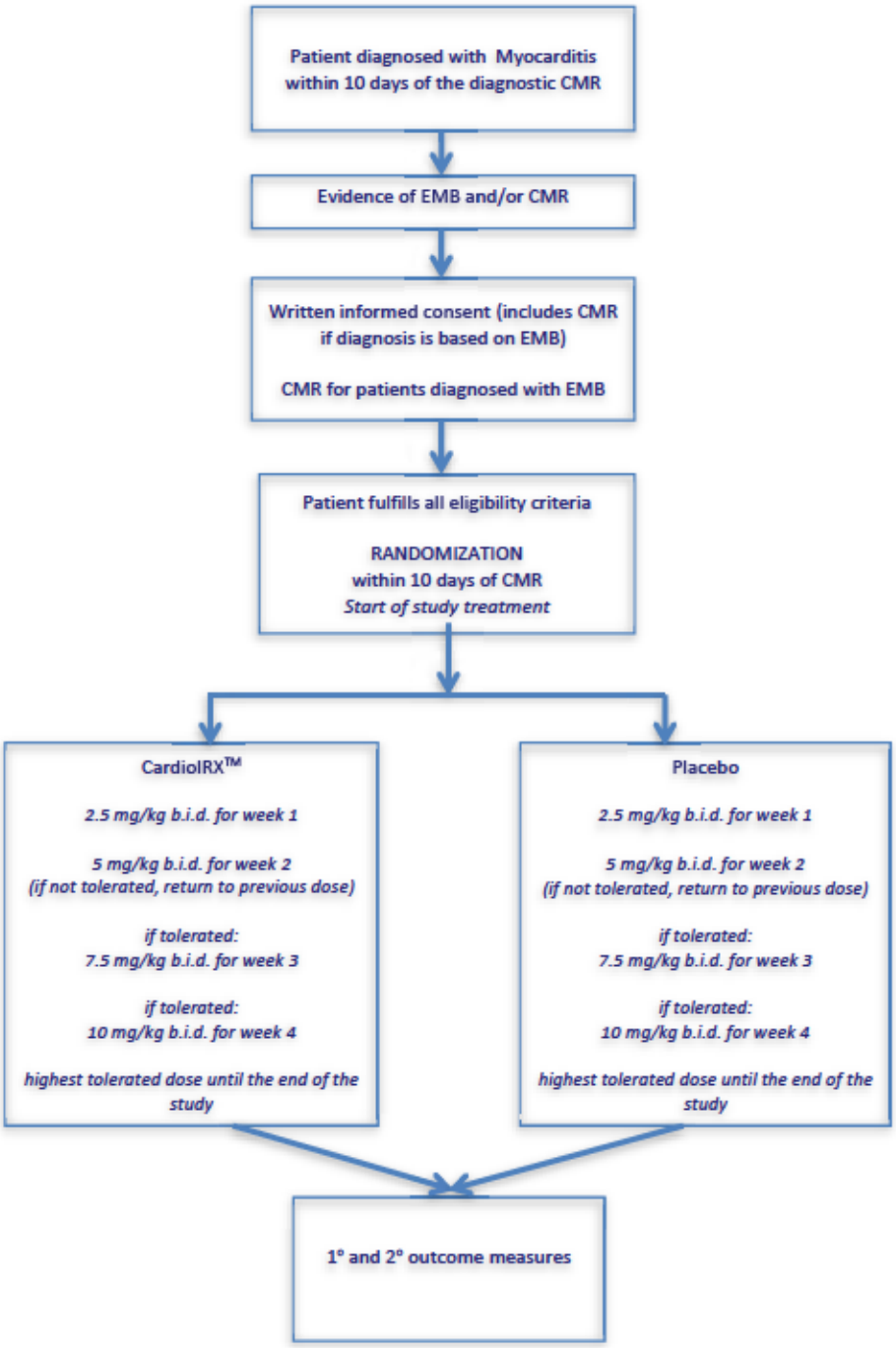
Also, because CardiolRx™ is known to inhibit the metabolism of certain other drugs, new symptoms or findings may represent toxicity from a concomitant medication that had previously been well tolerated. Please refer to Section 6.3 of the Investigator Brochure (IB) and to Appendix 17.9.

Drugs that are known to prolong QT intervals must not be started during the study (Appendix 17.10).

7 STUDY PLAN


Patient diagnosed with Myocarditis within 10 days of the diagnostic CMR
Evidence of EMB and/or CMR
Written informed consent (includes CMR if diagnosis is based on EMB)
CMR for patients diagnosed with EMB
Patient fulfills all eligibility criteria
RANDOMIZATION
within 10 days of CMR
Start of study treatment
CardiolRX™
2.5 mg/kg b.i.d. for week 1
5 mg/kg b.i.d. for week 2
(if not tolerated, return to previous dose)
if tolerated:
7.5 mg/kg b.i.d. for week 3
if tolerated:
10 mg/kg b.i.d. for week 4
highest tolerated dose until the end of the study
Placebo
2.5 mg/kg b.i.d. for week 1
5 mg/kg b.i.d. for week 2
(if not tolerated, return to previous dose)
if tolerated:
7.5 mg/kg b.i.d. for week 3
if tolerated:
10 mg/kg b.i.d. for week 4
highest tolerated dose until the end of the study
1° and 2° outcome measures

7 STUDY PLAN


Patient diagnosed with Myocarditis within 10 days of the diagnostic CMR
Evidence of EMB and/or CMR
Written informed consent (includes CMR if diagnosis is based on EMB)
CMR for patients diagnosed with EMB
Patient fulfills all eligibility criteria
RANDOMIZATION
within 10 days of CMR
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(if not tolerated, return to previous dose)
if tolerated:
7.5 mg/kg b.i.d. for week 3
if tolerated:
10 mg/kg b.i.d. for week 4
highest tolerated dose until the end of the study
Placebo
2.5 mg/kg b.i.d. for week 1
5 mg/kg b.i.d. for week 2
(if not tolerated, return to previous dose)
if tolerated:
7.5 mg/kg b.i.d. for week 3
if tolerated:
10 mg/kg b.i.d. for week 4
highest tolerated dose until the end of the study
1° and 2° outcome measures

8 INVESTIGATIONAL PRODUCTS, DOSE AND DURATION OF TREATMENT

8.1 Investigational Product

CardiolRx™ is pharmaceutically produced. It contains cannabidiol oil 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:

- Week 1 (p.m. dose of Day 1 to a.m. dose of Day 7):
  2.5 mg/kg of body weight b.i.d. CardiolRx™ or placebo
- Week 2 (p.m. dose of Day 7 to a.m. dose of Day 14):
  5 mg/kg of body weight b.i.d. CardiolRx™ or placebo
- Week 3 (p.m. dose of Day 14 to a.m. dose of Day 21):
  7.5 mg/kg of body weight b.i.d. CardiolRx™ or placebo
- Week 4 to end of treatment period (p.m. dose of Day 21 to a.m. dose of last day of treatment period at week 12):
  10 mg/kg of body weight b.i.d. CardiolRx™ or placebo
- The morning and evening doses should be taken within an 6 – 18-hour window of each other

If the next higher dose is not tolerated, the patient should return to the last tolerated dose. The highest tolerated dose should be administered until the end of the treatment period (12 weeks post randomization).

8.3 Study Treatment Return and Reconciliation

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

8.4 Supply, Packaging, Labelling and Storage

8.4.1 Supply and Packaging

The study drug will be provided in 30 ml bottles. New bottles will be handed out at each visit up to week 8.

8.4.2 Labelling and Storage

All investigational drugs 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 as follows:

- Room temperature 15°C - 25°C (59°F - 77°F) or refrigerated between 2°C - 8°C (36°F - 46°F). 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 study supplies need to be protected from light (to be kept in closed cartons or boxes) and stored in an upright position to prevent leakage.

9 CONDUCT OF THE STUDY

9.1 Scheduling of Study Procedures

Patients diagnosed with acute myocarditis by an EMB or a CMR will be screened within 10 days of the diagnostic CMR. Informed consent will be obtained at this point. For patients who have been diagnosed using an EMB, a CMR needs to be performed as well (within 10 days of randomization), which will be included in the ICF.

Baseline assessments ≤ 3 days from randomization
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
- Vital signs, including heart rate (HR), blood pressure, height, and weight
- 12-lead ECG
- NYHA classification
- KCCQ
- C-SSRS
- Local laboratory assessments, including Complete Blood Count (CBC), glucose, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR, pregnancy test (in women with childbearing potential only), hs-troponin
- Retention of frozen plasma for central analysis of hs-troponin, NT-proBNP, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2])
- Retention of frozen plasma for central analysis of CBD levels

Randomization and start of study medication should occur after all baseline assessments have been completed and all eligibility criteria are met in the evening of Day 1, within 10 days of the diagnostic CMR assessment.

1 week post randomization (+/- 2 days)
The following evaluations will be performed at 1 week post randomization:

- Vital signs, including HR, blood pressure and weight
- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours)
- Local laboratory assessments, including AST/ALT, alkaline phosphatase, bilirubin
- Retention of frozen plasma for central analysis of hs-troponin, NT-proBNP, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2])
- AE and SAE recording
- Recording of changes in concomitant medications

- Study drug dose adjustment and accountability
- New bottles of study medication will be dispensed

2 weeks post randomization (+/- 2 days)

The following evaluations will be performed at 2 weeks post randomization:

- Vital signs, including HR, blood pressure and weight
- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours)
- Local laboratory assessments, including CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR
- Retention of frozen plasma for central analysis of hs-troponin, NT-proBNP, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2])
- AE and SAE recording
- Recording of changes in concomitant medications
- Study drug dose adjustment and accountability
- New bottles of study medication will be dispensed

3 weeks post randomization (+/- 2 days)

The following evaluations will be performed at 3 weeks post randomization:

- Clinical assessment
- Vital signs, including HR, blood pressure and weight
- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours)
- Local laboratory assessments, including AST/ALT, bilirubin
- Retention of frozen plasma for central analysis of hs-troponin, NT-proBNP, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2])
- Retention of frozen plasma for central analysis of CBD levels
- AE and SAE recording
- Recording of changes in concomitant medications
- Study drug dose adjustment and accountability
- New bottles of study medication will be dispensed

4 weeks post randomization (+/- 2 days)

The following evaluations will be performed at 4 weeks post randomization:

- Vital signs, including HR, blood pressure and weight
- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours)
- Local laboratory assessments of AST/ALT and bilirubin
- Retention of frozen plasma for central analysis of hs-troponin, NT-proBNP, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2])
- AE and SAE recording
- Recording of changes in concomitant medications
- Study drug dose adjustment and accountability
- New bottles of study medication will be dispensed

6 weeks post randomization (+/- 3 days)

The following evaluations will be performed at 6 weeks post randomization:

- Clinical assessment
- Vital signs, including HR, blood pressure and weight
- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours)
- NYHA classification
- Local laboratory assessments, including CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR
- Retention of frozen plasma for central analysis of hs-troponin, NT-proBNP, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2])
- Retention of frozen plasma for central analysis of CBD levels
- AE and SAE recording
- Recording of changes in concomitant medications
- Study drug dose adjustment and accountability
- New bottles of study medication will be dispensed

8 weeks post randomization (+/- 3 days)

The following evaluations will be performed at 8 weeks post randomization:

- Vital signs, including HR, blood pressure and weight
- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours)
- Local laboratory assessments of AST/ALT and bilirubin
- AE and SAE recording
- Recording of changes in concomitant medications
- Study drug dose adjustment and accountability
- New bottles of study medication will be dispensed

12 weeks post randomization (+/- 4 days)

The following evaluations will be performed at 12 weeks post randomization:

- CMR
- Clinical assessment
- Vital signs, including HR, blood pressure, and weight
- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours)
- NYHA classification
- KCCQ
- C-SSRS
- Local laboratory assessments, including CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR
- Retention of frozen plasma for central analysis of hs-troponin, NT-proBNP, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2])
- Retention of frozen plasma for central analysis of CBD levels
- AE and SAE recording
- Recording of changes in concomitant medications
- Study drug accountability

13 weeks post randomization (+/- 4 days)

The following evaluations will be performed at 13 weeks post randomization:

- Clinical assessment
- Vital signs, including HR, blood pressure, and weight
- 12-lead ECG
- NYHA classification
- Local laboratory assessments, including CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR
- AE and SAE recording
- Recording of changes in concomitant medications

9.2 Clinical Procedures and Safety Evaluations

9.2.1 Informed Consent

Patients with evidence of myocardial inflammation by CMR or biopsy who meet all the eligibility criteria 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. The patients will also be asked for permission to allow for their diagnostic CMR data and, if applicable, the biopsy data, to be included in the study. If the diagnosis was based on an EMB, the patient will need to have a CMR to collect all required baseline CMR data. For these patients, the CMR will be included in the ICF. 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, and at all follow-up visits.

The ECG after randomization and start of study medication up to week 12 will be recorded at approximately 5 hours (time window 3.5 – 6 hours) post-morning dose (T_{max}) to surveil for deleterious effects on ECG intervals (particularly the QTc interval) and rhythm. Drug titration will be dependent on investigator or designate interrogation of the ECGs and the absence of abnormalities on those ECGs.

The QT interval can be obtained from the automated measurements of the ECG recorder unless the data quality is poor. In this case, 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 / √ 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.

The presence of a bundle branch block (BBB) 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 Medical History

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

9.2.5 Clinical Assessment

A routine clinical assessment is required at baseline, at 3, 6, 12 and 13 weeks. Any abnormality must be recorded.

9.2.6 Vital Signs, Body Height and Weight

Vital signs including blood pressure and heart rate and body weight will be recorded at baseline, after 1, 2, 3, 4, 6, 8, 12 and 13 weeks. Body height will be recorded at baseline.

9.2.7 NYHA Classification

NYHA classification will be recorded at baseline, at 6, 12 and 13 weeks. Please refer to Appendix 17.3 for definitions.

9.2.8 Concomitant Treatment

Concomitant medications will not be altered for the purpose of this trial. Guidelines for concomitant treatment are given in Section 6.7 of this protocol.

All changes in concomitant medications during the study must be recorded, as must those started before randomization and continued thereafter.

9.2.9 Laboratory Tests

9.2.9.1 Local Laboratory Tests

Local laboratory tests include CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, glucose, INR, pregnancy test (female patients of childbearing potential only), as well as hs-troponin (at baseline only). Please see Appendix 17.2 for the exact schedule of all laboratory tests.

9.2.9.2 Additional Laboratory Tests

In addition to local laboratory tests, the study protocol will require the following tests to be performed and analyzed by a central laboratory: hs-troponin, NT-proBNP, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2]).

Further blood samples will also be retained frozen for central analysis of plasma levels of CBD.

Please see Appendix 17.2 for the exact schedule of all laboratory tests.
All samples will be stored at -70C at the sites and will be shipped to the Central Laboratory at regular intervals.

9.2.10 Cardiac Magnetic Resonance Imaging (CMR)

All patients will undergo a CMR before study start and another CMR 12 weeks after randomization. The standardized examination protocol (Appendix 17.4) will include LVEF, LVEDV, LVESV, LAESV, ECV, GLS, LV mass, LGE extent and edema. All images will be analyzed centrally at a Central CMR Core Laboratory (McGill University Health Centre).

All recordings need to be sent to the CMR Core Laboratory to establish that both primary endpoints and the LVEF can be analyzed before the patient can be randomized.

9.2.11 Quality of Life Questionnaire

All patients will be asked to complete the KCCQ (Appendix 17.5) at baseline and at week 12 post randomization.

9.2.12 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 week 12.

The questionnaire must be administered by an investigator or other individual that is suitably qualified by education or training. See Appendix 17.6 for a sample C-SSRS - Baseline/Screening version assessment and Appendix 17.7 for a sample 12-week post-dose C-SSRS assessment.

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

9.2.13 Management of AEs

9.2.13.1 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 investigational product, whether or not considered related to the investigational product.

Adverse events 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 Drug-Induced Liver Injury (DILI) is also considered an important medical event. (See Section 9.2.13.3 for the definition of potential DILI.)

All SAEs experienced by a patient after informed consent has been obtained must be reported to SOCAR Research SA (SOCAR) within 24 hours of the site's awareness of the event.

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 *SAE 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 adverse event should be documented.

9.2.13.2 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 after product administration, the investigational product will be permanently discontinued and the pregnancy will be reported to SOCAR within 24 hours of the site's awareness of the event. 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.

9.2.13.3 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 investigator is to arrange for the patient to return to the investigational site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, bilirubin and alkaline phosphatase, detailed history, and clinical assessment. Patients are to be followed in this way until all abnormalities have normalized (in the investigator's opinion) or returned to the baseline state. If the patient cannot return to the investigational site, repeat assessments could be performed at a local laboratory (and the results are then to be sent to SOCAR by the investigator).

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.

9.2.13.4 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.

9.2.13.5 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 heart

failure and other CV 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 Drug-Drug Interactions (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 17.9).

10 CRITERIA FOR EVALUATION OF STUDY RESULTS

10.1 Criteria for Evaluation of Efficacy

10.1.1 Primary Efficacy Outcome

The primary outcome of this study is the difference between the active and the placebo groups in the means of both ECV and GLS, as measured by CMR at 12 weeks post randomization.

10.1.2 Secondary Efficacy Outcome

The secondary efficacy outcome of this study is the difference between the active and the placebo groups in the means of LVEF, as measured by CMR at 12 weeks post randomization.

10.1.3 Other Efficacy Outcomes

Other efficacy outcomes are listed in Section 4.1.5.

The results of the findings for these outcomes are supportive and not confirmatory on their own. Therefore, the effect of the randomly allocated study treatment on the additional outcomes 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 Modified Intention-to-Treat (mITT) Population

The primary analysis will be performed on the mITT population. All patients who were randomized and had the confirmed diagnosis of myocarditis by the CMR Core laboratory (based on the baseline CMR) will be included in the mITT analysis.

10.3.2 Intention-to-Treat (ITT) Population

All patients who were randomized will be included in the ITT analysis.

10.3.3 Safety Population

All patients who received at least one dose of study medication will be included in the safety analyses.

11 STATISTICAL METHODS

11.1 Sample Size Estimation

For the sample size estimation, we assume 80% power and a two-sided alpha of 0.025 (adjusted for multiplicity). Furthermore:

	Estimated means at 12 weeks CBD group	Estimated means at 12 weeks Placebo group	Expected Difference between CBD and Placebo	Assumed standard deviation	N per group (Total)
ECV(Isaak et al. 2022)	26.6	32	9.4	+/-7.8	40 (80)
GLS(Isaak et al. 2022)	-24.9	-21.1	3.8	+/-5.5	40 (80)

With an estimated 25% missing follow-up data, 50 patients per group (100 patients in total) are required.

Consideration will be given to adjust the study design after 50% of the patient have been randomized, should the standard deviations of the two primary endpoint parameters differ from the assumption above. This would be carried out in a blinded fashion. If the assumed standard deviations are much higher than expected, the sample size may be adjusted.

11.2 Outcome Analyses

11.2.1 Primary Efficacy Analysis

For both primary outcomes, the means in ECV and GLS at 12 weeks will be compared between the active and the placebo groups, applying an ANCOVA procedure, adjusted for baseline means.

The two primary outcomes will be considered statistically significant following the Hochberg Procedure.(Benjamini and Hochberg 1995)

11.2.2 Secondary Efficacy Analysis

For the secondary efficacy analysis, the means in LVEF at 12 weeks will be compared between the active and the placebo groups, applying an ANCOVA procedure, adjusted for baseline means.

11.2.3 Sensitivity Analyses

Sensitivity analyses will be performed (for the primary and secondary analyses) on the ITT population.

11.2.4 Other 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.

The differences in CMR parameters and other continuous secondary outcomes from baseline to 12 weeks post randomization between the two treatment groups will be analyzed using an ANCOVA. Treatment effect estimates and 95% confidence intervals will be determined.

The changes in hs-troponin, in NT-proBNP, in inflammatory markers and in endothelial markers from baseline to 12 weeks will be analyzed using an AUC analysis using all available time points.

Binary outcomes will be compared using a chi-square test. The differences in proportions experiencing these outcomes will be estimated, along with 95% confidence intervals.

11.3 Safety Analyses

The difference in continuous outcomes will be analyzed as described above in Section 11.2.2.

For dichotomous safety outcomes, the difference in proportions experiencing these will be estimated, with 95% confidence intervals.

11.4 Interim Analyses

No Interim analysis is planned for this trial.

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
- LVEF < 50% vs LVEF ≥ 50%
- Males vs. females
- Baseline diabetes mellitus (DM) vs. no DM
- Baseline HF vs. no HF
- Troponin rise vs. no troponin rise

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 outcomes, additional tipping point analyses may be considered should the above analysis be statistically significant at the 5% level.

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 Contract Research Organization (CRO)

SOCAR Research SA, Nyon, Switzerland (SOCAR) is the appointed CRO to be responsible for overall study management, including preparation of all study material and procedures, in-house and on-site data monitoring, data handling and safety reporting, data quality assurance, and statistical reporting as well as for the maintenance of the trial master file. SOCAR will also be responsible for organization of meetings, site initiation and training, on-site monitoring and study close-out. SOCAR will work with other CROs but holds the overall responsibility for the trial management.

SOCAR will issue regular progress reports and newsletters to be sent to investigators and committees.

12.3 Steering Committee

A Steering Committee will be appointed, which will include the Study Chair and a minimum of four investigators participating in the trial. 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, the Core Laboratory directors, and from SOCAR.

12.4 Data Safety and Monitoring Committee (DSMC)

An independent DSMC will be established. The committee will consist of at least two cardiologists and a statistician who are not otherwise associated with the study. The DSMC will conduct routine reviews of accumulating trial data in order to make recommendations concerning safety concerns and the appropriateness of continuing the study, as documented in the DSMC Charter.

12.5 Core Laboratory for CMR

All CMR assessments will be interpreted according to previously established criteria in a CMR Core Laboratory (McGill University Health Centre, Montreal, Canada); please refer to Appendix 17.4.

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 SOCAR throughout the duration of study, and up to 10 years after the study is complete. An encrypted compact disc of the tabulated study data will be stored at SOCAR 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 and/or On-site Monitoring

SOCAR is responsible for monitoring according to applicable local Good Clinical Practice (GCP) standards and International Conference on Harmonization (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 In-house Monitoring

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

13.3.3 Audit/Inspection

The Sponsor, SOCAR 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 SOCAR 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 CRO(s), 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, SOCAR or a designee and/or regulatory agencies 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 SOCAR. 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.
SOCAR 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 9.2.13 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, SOCAR 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 SOCAR 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 SOCAR and/or the Sponsor in strict confidence.

14.10 Direct Access to Source Data/Documents

The investigator shall supply the Clinical Research Associate (CRA), SOCAR, the Sponsor and/or regulatory agencies 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 will be registered on http://clinicaltrials.gov prior to patient enrolment.

15 STUDY TIMELINES

Eligible patients will be randomized and will be followed for 13 weeks. We estimate the following: a recruitment period of 15 months, time for data collection and cleaning 3 months, database lock, analysis and reporting 3 months, resulting in a total study time of approximately 24 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.

CARDIOL THERAPEUTICS

17.2 Schedule of Study Procedures

	Days before randomization		Weeks after randomization							
Test	≤ 10	≤ 3	1	2	3	4	6	8	12	13
Review of diagnostic CMR[1] by Core lab	X								X	
Consent[3]		X								
Clinical assessment		X			X		X		X	X
Demographics		X								
Medical History		X								
Vital Signs[4]		X	X	X	X	X	X	X	X	X
ECG		X	X	X	X	X	X	X	X	X
NYHA classification		X					X		X	X
KCCQ		X							X	
C-SSRS		X							X	
Randomization[5]		X								
Study medicationx[6]		XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX								
Study RX dose adjustment and accountability			X	X	X	X	X	X	X[7]	
Concomitant Rx		X	X	X	X	X	X	X	X	X
AE and SAE recording[8]		XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX								
	Days before randomization		Weeks after randomization							
Laboratory		≤ 3	1	2	3	4	6	8	12	13
Local Laboratory[9]										
CBC		X		X			X		X	X
Glucose		X								
ALT/AST		X	X	X	X	X	X	X	X	X
Alkaline Phosphatase		X	X	X			X		X	X
Bilirubin		X	X	X	X	X	X	X	X	X
Creatinine/ eGFR		X		X			X		X	X
INR		X		X			X		X	X
Pregnancy Test[10]		X								
Hs-tropnin[11]		X								
Central Laboratory[12]										
Hs-troponin		X	X	X	X	X	X		X	
NT-proBNP		X	X	X	X	X	X		X	
Ferritin		X	X	X	X	X	X		X	
IL-1 beta, IL-6, IL-10, IL-18		X	X	X	X	X	X		X	
TNF-alpha		X	X	X	X	X	X		X	
Hs-CRP		X	X	X	X	X	X		X	
sVCAM-1		X	X	X	X	X	X		X	
TGF-beta [beta 1 and beta 2]		X	X	X	X	X	X		X	
Retention of frozen plasma for CBD levels		X			X		X		X	

[1] Diagnostic CMR in all patients within 10 days of randomization
[3] Patient consent form including CMR for patients diagnosed by EMB, request to use diagnostic CMR and/or biopsy data
[4] Vital signs include heart rate, blood pressure and weight; height at baseline
[5] Randomization after all baseline assessments, including local laboratory tests, have been completed
[6] Start of study drug in the evening of Day 1 after randomization according to treatment schedule
[7] At final visit accountability only
[8] Adverse Event recording starts after informed consent is obtained
[9] All local laboratory assessments at baseline, including hs-troponin, to be performed before randomization
[10] Pregnancy test in women with childbearing potential only.
[11] Hs-troponin for diagnostic evaluation assessed locally at baseline only
[12] Retention of frozen plasma for central laboratory analyses

17.3 New York Heart Association (NYHA) Classification

Class	Patient Symptoms
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

http://www.abouthf.org/questions_stages.htm

17.4 CMR Protocol

Executive Summary

CBD in Acute Myocarditis Trial
CMR Protocol

Team

Core Lab Director: Matthias Friedrich, McGill University Health Centre
Project Management: Adonis Rodaros, McGill University Health Centre

Study Trial Objectives and Design

The CBD in Acute Myocarditis Trial aims to investigate the effect of CBD application in patients with clinically and imaging-verified acute myocarditis.

Rationale for Using CMR

Cardiac Magnetic Resonance (CMR) is well established as the non-invasive gold standard for the quantitative assessment of the heart. CMR is also the prime non-invasive tool for identifying myocardial inflammation and its consequence (edema, necrosis, scar, regional or global dysfunction, ventricular dilatation, heart failure). [1] CMR allows for a comprehensive qualitative and quantitative assessment of LV function and morphology, function, as well as markers for inflammatory changes in the myocardium. There are established diagnostic criteria (Lake Louise Criterai for CMR in Myocardial Inflammation), that have recently been updated.[2]
In order to provide evidence for acute myocardial inflammation, the results require one criterion reflecting myocardial edema and one reflecting myocardial injury. In cases with a string clinical suspicion, one criterion may be considered sufficient to corroborate the diagnosis. [2] There are standardized evaluation procedures for all markers. [3]

CMR Core Lab

CMR Core Lab

- The MUHC CMR Core Lab will serve as the core lab for this trial.
- Standard Operating Procedures will be applied according to the protocol of the Study and MUHC standards.
- The analysis for this trial is blinded to the clinical and other data from patients.
- Image data and accompanying information will be kept anonymized/de-identified.

Reader

- CMR reader with significant (>12 months) experience in the evaluation procedure.

CMR analysis

- Analyses will be performed according to the standard operating procedures of the CMR Core Lab and according to the study protocol

Software and Data Format

- cvi42 version 5.13 (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 as CSV data.

CMR Image Quality Assessment

Before the evaluation, the submitted scan data are assessed for completeness (all required images are available and can be evaluated). All images will be assessed 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 in the myocardium) are not significantly distorted by field inhomogeneities, motion artifacts, or other artifacts.
- An *Image Submission Form* will be developed by the core lab 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/m^2 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 this trial, it will be reported to the Safety committee of the trial.

Data Transfer and storage
Images will be transferred via a secured internet transfer protocol. The transfer is done via https secure protocol. The site will a login and password to be able to use the data transfer tool. Once the images will be stored in the research MUHC PACS. These images will then be sent to the CMR MUHC Core Lab for acceptability review and analysis.

Montreal, December 18, 2024

References:

1. *Blisset S, Chocron Y, Kovacina B. Afilalo J. Diagnostic and prognostic value of cardiac magnetic resonance in acute myocarditis: a systematic review and meta-analysis. Int J Cardiovasc Imaging Spinger Netherlands; 2019;35:2221-2229*

2. *Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P, Friedrich MG. Cardiovascular Magnetic Resonance in Nonischemic Myocardial inflammation: Expert Recommendations. J Am Coll Cardiol 2018;72:3158-3176.*

3. *Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, Kim RJ, Knobelsdorff-Brenkenhoff von F, Kramer CM, Pennell DJ, Plein S, Nagel E. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) Board of Trustees Task Force on Standardized Post Processing. J Cardiovasc Magn Reson 2013;15:35.*

17.5 KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE (KCCQ)

The KC Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	❑	❑	❑	❑	❑	❑
Showering/Bathing	❑	❑	❑	❑	❑	❑
Walking 1 block on level ground	❑	❑	❑	❑	❑	❑
Doing yardwork, housework or carrying groceries	❑	❑	❑	❑	❑	❑
Climbing a flight of stairs without stopping	❑	❑	❑	❑	❑	❑
Hurrying or jogging (as if to catch a bus)	❑	❑	❑	❑	❑	❑

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
❑	❑	❑	❑	❑	❑

Original US English

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
❑	❑	❑	❑	❑	❑

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
❑	❑	❑	❑	❑	❑

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

Original US English

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
❑	❑	❑	❑	❑	❑

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
❑	❑	❑	❑	❑

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
❑	❑	❑	❑	❑

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
❑	❑	❑	❑	❑

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
❑	❑	❑	❑	❑

Original US English

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
❑	❑	❑	❑	❑

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	❑	❑	❑	❑	❑	❑
Working or doing household chores	❑	❑	❑	❑	❑	❑
Visiting family or friends out of your home	❑	❑	❑	❑	❑	❑
Intimate relationships with loved ones	❑	❑	❑	❑	❑	❑

Original US English

17.6 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. ***Have you made a suicide attempt?***	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
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* _____

17.7 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.)*

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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* _____

17.8 Drugs That Are Strong Inducers of CYP3A4 and CYP2C19

17.8.1 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

17.8.2 CYP2C19 Inducers

- Rifampin

17.9 Cannabidiol and Drug-Drug Interactions

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 17.8.**
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. This patient population maybe 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
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 – reduce dose/change medication	CYP2C8

	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 – monitor BP, adjust dose or change to other medication	UGT1A9

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 – monitor blood glucose and adjust dose.	CYP2C9
	Dapagliflozin	Improves glycemic control in Type 2 DM and improves HF	CYP1A2

		management. May cause hypoglycemia, hypotension, rapid weight loss, dehydration, worsen urinary tract infections – monitor blood sugar, adjust dose	
	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	Trimethidione	Assess for excessive adverse effects such as drowsiness, swelling of gums – Adjust dose or substitute other agent	CYP2C8
	Valproic Acid	Nausea and vomiting, drowsiness, dry mouth, transaminase elevations – monitor liver enzymes – adjust dose or change medication	CYP2C9
Anti-diarrheal	Loperamide	May cause dehydration, weakness, faintness, rapid	CYP2C8

		heart rhythm – discontinue if possible	
Antihistamine	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	CYP2C9

		irritation and bleeding and increase action of warfarin anti-coagulants – change to other anti-inflammatory	
	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	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.	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
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

17.10 Drugs that can prolong QTc intervals

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

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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

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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)	Hysingla&,¢ 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)	Nozinan and others
Levomethadone (levamethadone) (PR)	
Levomethadyl acetate (KR)	Orlaam
Levosulpiride (KR)	Levorid 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)	Terlipress 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

Note: Medicines on this list are reviewed on an ongoing basis to assure that the available evidence supports their 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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17.4 CMR Protocol

Executive Summary

CBD in Acute Myocarditis Trial
CMR Protocol

Team

Core Lab Director: Matthias Friedrich, McGill University Health Centre
Project Management: Adonis Rodaros, McGill University Health Centre

Study Trial Objectives and Design

The CBD in Acute Myocarditis Trial aims to investigate the effect of CBD application in patients with clinically and imaging-verified acute myocarditis.

Rationale for Using CMR

Cardiac Magnetic Resonance (CMR) is well established as the non-invasive gold standard for the quantitative assessment of the heart. CMR is also the prime non-invasive tool for identifying myocardial inflammation and its consequence (edema, necrosis, scar, regional or global dysfunction, ventricular dilatation, heart failure). [1] CMR allows for a comprehensive qualitative and quantitative assessment of LV function and morphology, function, as well as markers for inflammatory changes in the myocardium. There are established diagnostic criteria (Lake Louise Criterai for CMR in Myocardial Inflammation), that have recently been updated.[2]
In order to provide evidence for acute myocardial inflammation, the results require one criterion reflecting myocardial edema and one reflecting myocardial injury. In cases with a string clinical suspicion, one criterion may be considered sufficient to corroborate the diagnosis. [2] There are standardized evaluation procedures for all markers. [3]

CMR Core Lab

CMR Core Lab

- The MUHC CMR Core Lab will serve as the core lab for this trial.
- Standard Operating Procedures will be applied according to the protocol of the Study and MUHC standards.
- The analysis for this trial is blinded to the clinical and other data from patients.
- Image data and accompanying information will be kept anonymized/de-identified.

17.10 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

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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)	Hysingla&,¢ 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)	Nozinan and others
Levomethadone (levemethadone) (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

No[illegible] on this list are re[illegible] on an ongoing basis to assure [illegible] continued placement on [illegible], 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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