Clinical Study Protocol

Study Title:	**Impact of CardiolRx™ on Recurrent Pericarditis** An open label Pilot Study
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Protocol No. Cardiol 100-004

Impact of CardiolRx™ on Recurrent Pericarditis

An open label Pilot Study

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Title:	**Impact of CardiolRx™ on Recurrent Pericarditis**
Product:	**CardiolRx™**
Protocol No.:	**Cardiol 100-004**
Protocol Release Date:	June 03, 2022 v. 1.2 (Administrative changes) Amendment 1, July 09, 2022 Amendment 2, January 18, 2022

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 Recurrent Pericarditis** An open label Pilot Study
Diagnosis	Recurrent Pericarditis
Rationale	Patients with recurrent pericarditis who are refractory or intolerant to current therapeutic management options or who require long-term administration of corticosteroids to control their disease are particularly challenging to manage. The pathogenesis of pericarditis involves the activation of the inflammasome. CardiolRx™ (a pure cannabidiol [CBD] solution) is known to have anti-inflammatory properties, including modulation of inflammasome signaling. This pilot study is to assess the tolerance and safety of CardiolRx™ during the resolution of pericarditis symptoms, assess improvement in objective measures of disease, and during the extension period, assess the feasibility of weaning concomitant background therapy including corticosteroids while taking CardiolRx™.
Inclusion Criteria	The following inclusion criteria must be met to enroll a patient into this study: 1. Male or female 18 years of age or older 2. Diagnosis of at least two episodes of recurrent pericarditis*, 3. At least 1 day with pericarditis pain ≥4 on the 11-point Numerical Rating Scale (NRS) within prior 7 days 4. One of; a. C-Reactive Protein** (CRP) level ≥1.0 mg/dL within prior 7 days **OR** b. Evidence of pericardial inflammation assessed by delayed pericardial hyperenhancement on cardiac magnetic resonance imaging (CMR) 5. Currently receiving non-steroidal anti-inflammatory drugs (NSAIDs) and/or colchicine and/or corticosteroids for treatment of pericarditis (in any combination) in stable doses 6. Male patients 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. 7. 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. *Diagnosis of pericarditis according to the 2015 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al. 2015): At least two of: a. Pericarditic chest pain

	b. Pericardial rub c. New widespread ST-segment elevation or PR-segment depression according to electrocardiogram (ECG) findings d. Pericardial effusion (new or worsening) ** Conversion: 1 mg/dL CRP = 10 mg/L hs-CRP
Exclusion Criteria	Patients meeting any of the following criteria will be excluded from the study: 1. Diagnosis of pericarditis that is secondary to specific prohibited etiologies, including tuberculosis (TB); neoplastic, purulent, or radiation etiologies; post-thoracic blunt trauma (e.g., motor vehicle accident); myocarditis 2. Estimated glomerular filtration rate (eGFR) <30 mL/min at screening 3. 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 4. Sepsis, defined as documented bacteremia at the time of screening or other documented active infection 5. Prior history of sustained ventricular arrhythmias 6. History of QT interval prolongation 7. QTc interval > 500 msec (please refer to Section 9.2.3 for bundle branch block, bifascicular block and paced rhythm correction) 8. Current participation in any research study involving investigational drugs or device 9. Inability or unwillingness to give informed consent 10. Ongoing drug or alcohol abuse 11. On any cannabinoid during the past month 12. Women who are pregnant or breastfeeding 13. Current diagnosis of cancer, with the exception of non-melanoma skin cancer 14. Any factor, which would make it unlikely that the patient can comply with the study procedures 15. Showing suicidal tendency as per the Columbia Suicide Severity Rating Scale (C-SSRS), administered at screening 16. On digoxin and/or type 1 or 3 antiarrhythmics 17. On immunosuppressive therapy with any of the following: a. Rilonacept b. Anakinra c. Canakinumab d. Methotrexate e. Azathioprine f. Cyclosporine g. Intravenous immune globulin (IVIG)
Primary Efficacy Objective	The primary objective is to evaluate the effect of treatment with CardiolRx™ on recurrent pericarditis.
Primary Efficacy Endpoint	The primary efficacy endpoint is the change in patient-reported pericarditis pain using an 11-point NRS from baseline to 8 weeks.

Additional Efficacy Endpoints of Interest	- Pain score using 11-point NRS after 26 weeks of treatment - Percentage of patients with normalized CRP levels at 8 weeks (for patients with CRP ≥1.0 mg/dL at baseline) - Percentage of patients with pericarditis recurrence during the extension period (EP) - Percentage of patients with normalized CRP levels at 26 weeks (for patients with CRP ≥1.0 mg/dL at baseline) - Time to CRP normalization for patients with CRP ≥1.0 mg/dL at baseline - CRP change from baseline at 26 weeks (%)
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 C-SSRS as well as changes in laboratory parameters, including liver function parameters and INR as well as ECG intervals and rhythm during the 26-week study period.
Number of Patients/Sites:	Approximately 25 patients will be enrolled in multiple centers.
Scheduled Duration of Study:	Estimated 4 months site setup, 12 months recruitment, 26 weeks of follow-up, approximately 2 months data cleaning and database lock, 2 months for analysis and report, for a total of approximately 26 months.
Design & Methodology	Multi-center, open label Pilot Study. Patients who present with recurrent pericarditis will be screened and informed consent obtained. Baseline assessments include the following: Clinical assessment, including vital signs, highest NRS pain score within the past 7 days of Day 1, 12-lead ECG; C-SSRS as well as hematology and blood chemistry and a pregnancy test for women with child-bearing potential. Concomitant medications are recorded as well as any (S)AEs after informed consent has been obtained. Study treatment will be initiated in eligible patients in the evening of Day 1, after all baseline assessments are completed. Oral administration (accompanied by food) is as follows: • Initial starting dose (Day 1 p.m. dose to Day 3 a.m. dose): 5 mg/kg of body weight CardiolRx™ b.i.d. • Day 3 p.m. dose to Day 10 a.m. dose: 7.5 mg/kg of body weight CardiolRx™ b.i.d. • Day 10 p.m. dose to end of study (a.m. dose on Week 26): 10 mg/kg of body weight CardiolRx™ b.i.d. • The morning and evening doses should be taken minimally 6 hours and maximally 18 hours between each intake. If the next higher dose after each study drug increase is not tolerated, the dose will be reduced to the previous tolerated dose.

	Unless contraindicated in the opinion of the investigator, after 8 weeks of study treatment, patients will enter an 18-week EP, in which they continue study treatment while their concomitant medications to treat pericarditis will be weaned. Follow-up Procedures At every assessment before study drug dose increase the patient will be re-evaluated. This includes a twelve-lead ECG 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 to 7.5 and 10 mg/kg b.i.d. will be dependent on investigator or designate interrogation of the ECGs and the absence of clinically significant abnormalities on those ECGs. Concurrent medication changes and (S)AEs will be recorded at all visits. Vital signs, blood chemistry including liver function tests, hematology as well as INR assessments will be carried out at selected visits (see detailed schedule in Appendix 17.2). Final efficacy assessments will take place after 26 weeks of study treatment and include a clinical assessment, vital signs, pain score NRS, a 12-lead ECG, the C-SSRS, as well as laboratory assessments. For patients who do not enter the EP, Final assessments will be done after 8 weeks.
Concomitant Treatments	Patients must be on Standard of care (SOC) treatments with NSAIDs, colchicine, or corticosteroids (in any combination) prior to Day 1. These SOC treatments will be weaned during the 18 weeks EP, as described in Section 6.6. Patients will not be allowed to be on immunosuppressive therapy with rilonacept, anakinra, canakinumab, methotrexate, azathioprine, cyclosporine, mycophenolate and/or IVIG and cannot take any cannabinoids during the study period or strong inducers of CYP3A4 and CYP2C19 (see Appendix 17.7). Drugs that are known to prolong QT intervals must not be started during the trial. (Appendix 17.6)
Statistical Analysis Approach	Given the small sample size and the design of the study (no placebo comparison), no inferential statistical analyses are planned. Depending on their distribution, continuous variables will be expressed as mean ± standard deviation (SD) or as median (Interquartile range [IQR]). Categorical variables will be expressed in counts with percentages. For all continuous variables, including the NRS pain score, the change from baseline will be presented as summary statistics. For categorical variables, summary statistics will be calculated.

2 LIST OF ABBREVIATIONS

Abbreviation	Definition
5-HT1A	5-Hydroxy Tryptamine (Serotonin) Receptor 1A
AE	Adverse Event
ALT	Alanine Aminotransferase
a.m.	Morning
ASC	Apoptosis-associated speck-like protein containing a caspase recruitment domain
AST	Aspartate Aminotransferase
ATP	Aadenosine triphosphate
BBB	Bundle Branch Block
b.i.d.	Twice a Day
BNP	Brain Natriuretic Peptide
CB1/CB2	Cannabinoid receptors 1/2
CBC	Complete Blood Count
CBD	Cannabidiol
CMR	Cardiac Magnetic Resonance Imaging
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DOX	Doxorubicin
EAM	Experimental Autoimmune Myocarditis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDCF	Electronic Data Clarification Form

Abbreviation	Definition
EDV	End Diastolic Volume
eGFR	Estimated Glomerular Filtration Rate
EP	Extension period
ESC	European Society of Cardiology
ESR	Erythrocyte sedimentation rate
eTMF	Electronic trial master file
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practices
GI	Gastrointestinal
GPR	G-Protein-coupled Receptor
hGMSCs	Human gingival mesenchymal stem cells
HFC	High-fat, high-cholesterol
HR	Heart Rate
Hs-CRP	High-sensitivity C-reactive protein
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFN-gamma	Interferon-gamma
IL-1 α	Interleukin 1-alpha
IL-1 β	Interleukin 1-beta
IL-6	Interleukin 6
INR	International Normalized Ratio
IRB/REB	Institutional Review Board/Research Ethics Board
IQR	Interquartile range
IVIG	Intravenous immune globulin
KCCQ	Kansas City Cardiomyopathy Questionnaire

Abbreviation	Definition
LBBB	Left Bundle Branch Block
LPS	Lipopolysaccharide
LVAD	Left ventricular assist device
MCP1	Monocyte Chemoattractant Protein-1
MCT	Medium-chain triglyceride
NF-κB	Nuclear factor kappa light chain enhancer of activated B cells
NLRP	Nod-Like Receptor Protein
NLR	NOD-like receptor
NOD	Nucleotide-binding and oligomerization
NRS	Numerical Rating Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
p.m.	Afternoon
PPAR-gamma	Peroxisome Proliferator-Activated Receptor Gamma
RBBB	Right Bundle Branch Block
ROS	Reactive oxygen species
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard Deviation
SOC	Standard of Care
TB	Tuberculosis
THC	Tetrahydrocannabinol
T_{max}	Time to Maximum Concentration
TNF- α	Tumor Necrosis Factor Alpha
NRF2	Nuclear factor erythroid 2-related factor 2
TRP	Transient Receptor Potential
ULN	Upper Limit of Normal
UVA	Ultraviolet rays A

Abbreviation	Definition
UVB	Ultraviolet rays B
WBC	White Blood Count

3 BACKGROUND

3.1 Description of Recurrent Pericarditis

Recurrent pericarditis is a disease characterized by a remitting-relapsing inflammation (or symptoms that fluctuate in severity) of the pericardium, a thin tissue sac surrounding the heart.(A. L. Klein, Imazio, et al. 2021)

Pericarditis often causes chest pain, which can be sharp. This chest pain worsens when patients take a deep breath. Etiologies of pericarditis include infectious causes (viral, bacterial, fungal and parasitic) and non-infectious causes (idiopathic, autoimmune, neoplastic, metabolic, traumatic, post-surgical and drug-related)(Massimo Imazio et al. 2010; Zayas et al. 1995). In 80% of cases in developed countries, the cause of pericarditis is either post-viral or "idiopathic" in that it cannot be attributed to a specific condition.(Mauro et al. 2021)

Diagnosis of pericarditis is based on the presence of typical chest pain (improved by sitting up and leaning forward) along with fever, pericardial friction rub, electrocardiographic changes, pericardial effusion, or elevated levels of inflammation markers [white blood cell count (WBC), CRP, or erythrocyte sedimentation rate (ESR)]. The ESC Guidelines for the Diagnosis and Management of Pericardial Diseases define an acute pericarditis episode as the presence of at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rubs, new widespread ST-segment elevation or PR-segment depression based on ECG findings, and pericardial effusion (new or worsening). Elevations of certain markers of inflammation (i.e., CRP, ESR and WBC) or evidence of pericardial inflammation by an imaging technique, e.g., CMR are used as supportive findings.(Adler et al. 2015)

For most patients, pericarditis manifests as a single episode that lasts a few days to several weeks, and symptoms are resolved through conventional treatments such as NSAIDs with or without colchicine.

There are, however, some patients who do not experience long-term symptom resolution after an acute pericarditis episode. Up to 30% of patients experience recurrent pericarditis within 18 months when a subsequent episode occurs following a symptom-free period of at least 4 weeks. Beyond the first recurrence, the clinical picture of recurrent pericarditis varies broadly, with some patients responding well to conventional therapy and having no further recurrence. By contrast, 25% to 50% of patients who have experienced a first recurrence will experience additional recurrences, and among patients who have experienced ≥2 recurrences, 20% to 40% are expected to have subsequent episodes.(A. Klein et al. 2021)

The etiology of recurrent pericarditis is presumed to be an immune-mediated phenomenon related to an incomplete treatment of the disease rather than to a recurrent viral infection. (Chiabrando et al. 2020) This is supported by the time to event,

the evidence of non-organ-specific antibodies, and the good response to corticosteroid therapy. Factors associated with an increased risk of recurrences are female sex, previous corticosteroid use, and frequent prior recurrences.

Although its pathogenesis is not completely understood, it has been hypothesized that pericarditis represents a stereotypical response to an acute injury of the mesothelial cells of the pericardium.(Buckley et al. 2018; Brucato et al. 2016) The trigger, an "irritant," such as a virus or cellular debris following a viral infection, may activate the NACHT, leucine-rich repeat, and pyrin domain-containing protein 3 (NLRP3) inflammasome, a macromolecular intracellular complex evolved to sense stress or injury and then trigger a local or systemic inflammatory response through the release of proinflammatory cytokines, such as interleukin (IL)-1β. The NLRP3 inflammasome is formed by the oligomerization of: 1) a sensor, namely NLRP3, which is a member of the NOD-like receptor (NLR) proteins; 2) a scaffold protein, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC); and 3) an effector, caspase-1, whose activation is strictly required for the activity of the inflammasome as it cleaves pro–IL-1β to the active IL-1β. IL-1α is another isoform of the IL-1 family that is released during cellular injury, functioning as an alarmin, and triggering the same inflammatory signaling as IL-1β.(Mauro et al. 2021)

A recent study (Mauro et al. 2021) described the presence of NLRP3 inflammasome expression in human pericardial specimens from patients with pericarditis. It also demonstrated that the phenotype of acute pericarditis—thickening of the pericardium, presence of an effusion, and inflammation associated with NLRP3 expression—can be reproduced in a mouse model with the instillation within the pericardial space of zymosan A, an activator of the NLRP3 inflammasome. Furthermore, drugs known to inhibit the NLRP3 inflammasome pathway (i.e., colchicine, NLRP3inh 16673-34-0, anakinra, and the rilonacept) were found to reduce all or most of the above-mentioned inflammatory effects.

3.2 Prevalence

Exact epidemiological data for acute pericarditis are lacking. The incidence was reported as 27.7 cases per 100,000 person-years in an urban area in Northern Italy, with concomitant myocarditis in about 15% of cases.(Massimo Imazio and Gaita 2017) Acute pericarditis is diagnosed in 0.2% of all cardiovascular (CV) in-hospital admissions and is responsible for 5% of emergency room admissions for chest pain in North America and Western Europe. (Spodick 2003; Massimo Imazio et al. 2010; 2004; Kytö, Sipilä, and Rautava 2014) Up to 30% of patients with an acute pericarditis experience a recurrence after an initial symptom-free period of 4 to 6 weeks.(Massimo Imazio et al. 2013)

The estimated prevalence of recurrent pericarditis in the US and Europe is 70,000 to 160,000 patients including approximately 8,000 to 21,000 patients who are refractory or intolerant to current therapies or who require long-term administration of corticosteroids

to control their disease.(Lazaros et al. 2016; Massimo Imazio et al. 2010; Khandaker et al. 2010; M. Imazio et al. 2008)

A recent retrospective US database analysis included newly diagnosed patients with recurrent pericarditis with ≥24 months of continuous history following their first pericarditis episode found that recurrent pericarditis of idiopathic or post-viral etiology has a US prevalence of about 37,000 cases, of which approximately half are expected to develop a complication or require a procedure within 2 years of diagnosis.(A. Klein et al. 2021)

3.3 Clinical Course

Within the population of recurrent pericarditis, some patients, including those with multiple recurrences or other serious complications, are at higher risk for adverse outcomes. Cremer et al (Cremer et al. 2016) have proposed a set of real–world clinical stages of pericarditis: acute, first recurrence, multiple recurrences, colchicine-resistant or steroid-dependent, and constrictive. While each stage is clearly defined clinically, the epidemiology of patients who experience multiple recurrences and/or recurrence plus complications is not well understood. Multiple recurrences and/or complications occur in up to one-third of patients with acute pericarditis, leading to increased morbidity, prolonged disease duration, impaired physical and mental health-related quality of life, and clinical complications. Complications related to pericarditis include serious and potentially life-threatening issues such as cardiac tamponade, constrictive pericarditis, or pericardial effusion. Patients who experience multiple recurrences and/or have serious complications or comorbidities may utilize substantial healthcare resources without necessarily experiencing clinical improvement.

3.4 Current Treatment Options

Currently, there are no US treatment guidelines for pericarditis or recurrent pericarditis; standard therapy consists of NSAIDs or aspirin with or without colchicine. Corticosteroids and other off-label immunosuppressants are used in patients with continued recurrence and inadequate response to conventional therapy.(Lotriionte et al. 2010) European guidelines indicate that corticosteroids should generally be avoided, as their use has been associated with increased risk of recurrence, particularly if the dose is tapered rapidly. In the most severe cases, pericardiectomy may be performed, although it does not always prevent recurrence. Among the patients with recurrent pericarditis with multiple recurrences and/or complications, disease burden is substantial and treatment options are currently inadequate.(Adler et al. 2015)

The potential of IL-1 inhibition was evaluated in a trial of the recombinant IL-1-receptor antagonist anakinra in a small number of patients with colchicine-resistant idiopathic recurrent pericarditis who had previously had pericarditis recurrence after the withdrawal of glucocorticoids; many of the patients continued using colchicine during that trial.(Brucato et al. 2016) A subsequent phase 2 trial of rilonacept, an IL-1α and IL-1β cytokine trap (A. L. Klein, Lin, et al. 2021), provided early evidence of resolution of

pericardial inflammation. The phase 3 trial RHAPSODY was then conducted to test the primary hypothesis that rilonacept would lead to a lower risk of pericarditis recurrence than placebo. The trial found that among the patients with recurrent pericarditis, rilonacept led to rapid resolution of recurrent pericarditis episodes and to a significantly lower risk of pericarditis recurrence than placebo after withdrawal of background therapy.(A. L. Klein, Imazio, et al. 2021) The only approved therapy for the treatment of recurrent pericarditis is rilonacept.

The clinical benefit seen with IL-1 inhibitors is hypothesized to be indirect evidence of the involvement of the NLRP3 inflammasome signaling in the pathophysiology of pericarditis.(Mauro et al. 2021)

3.5 Rationale

It is proposed that CardiolRx™ (a pure CBD oral solution), that is known to have anti-inflammatory properties, can treat the underlying inflammatory process and thereby favorably modify recurrent pericarditis.

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; Giuseppe Esposito et al. 2011; Saoirse Elizabeth O'Sullivan 2016) 5-Hydroxy Tryptamine (Serotonin) Receptor 1A (5-HT1A) (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).

Effects of Cannabidiol on the inflammasome:

While the exact molecular mechanisms by which cannabidiol modulates inflammasome signaling has not been investigated completely, the current evidence supports their importance as promising therapy to regulate inflammasome signaling.(Suryavanshi, Kovalchuk, and Kovalchuk 2020)

The first report on the direct effect of CBD on the inflammasome came in 2016 from a group of Italian researchers.(Libro et al. 2016) They treated human gingival mesenchymal stem cells (hGMSCs) for 24 h with CBD (5 mM) and performed gene expression analysis and immunocytochemistry. They discovered that CBD-treated hGMSCs suppressed NLRP3, caspase-1, and IL-18 at the gene and protein levels and inhibited NF-κB. As NF-κB is involved in the priming of the NLRP3 inflammasome, the

CBD treatment– induced inactive state of the NLRP3 inflammasome in hGMSCs suggested that CBD-treated gingival stem cells were more immunocompetent, avoiding the risk of inflammatory reactions and promoting survival. Mice fed with a high-fat, high cholesterol (HFC) diet for 8 weeks showed significantly higher expressions of NLRP3 inflammasome pathway proteins (NLRP3, ASC, IL-1β, and caspase-1) in the liver; these proteins were significantly attenuated by simultaneous treatment with CBD (5 mg/kg/day for 8 weeks). Similarly, the phosphorylation of NF-κB was significantly reduced in the liver of CBD-treated HFC mice compared to the non-treated group, corroborating the role of NF-κB in priming the NLRP3 inflammasome. To further confirm the role of the inflammasome in liver inflammation, the authors studied the effect of CBD on an LPS + ATP treated mouse macrophage cell line, confirming with *in vivo* data that the expressions of NLRP3, ASC, IL-1β, NF-κB, and caspase-1 were lower in CBD-treated cells. (Huang et al. 2019) Mouse microglial cells treated with LPS to simulate neuroinflammatory conditions exhibited a robust activation of pro-inflammatory cytokine repertoire, and CBD (1–10 mM) was able to suppress the secretion of IL-1β and inhibit the NF-κB signaling pathway.(Dos-Santos-Pereira et al. 2019).

In an *in vitro* skin inflammation model, human keratinocytes were treated with ultraviolet rays A and B (UVA and UVB) and treated with CBD (1 mM) for 24 h. CBD inhibited protein-protein interaction between nuclear factor erythroid 2-related factor 2 (Nrf2) and NF-κB in UVA- and UVB-treated skin cells. CBD increased NRF2 expression, leading to decreased reactive oxygen species (ROS), which in turn may have partially suppressed NLRP3 inflammasome activation by reducing NF-κB levels.(Jastrząb, Gęgotek, and Skrzydlewska 2019). Beta Amyloid induced neurotoxicity (G Esposito et al. 2007) and the severity of inflammatory colitis (Borrelli et al. 2009) were significantly suppressed by CBD treatment in mice partly due to inhibiting the expression and release of IL-1β.

A significant reduction of IL-1β by CBD treatment in a murine viral model of multiple sclerosis was also shown, suggesting its role in combating inflammation in multiple sclerosis. (Mecha et al. 2013) Recently, CBD was shown to inhibit NLRP3 inflammasome by reducing K+ efflux by binding to the P2X7 receptor in human monocytes.(Liu et al. 2020) Remarkably, the fact that only CBD (non-psychoactive), not tetrahydrocannabinol (THC) (psychoactive), was found to inhibit NFκB signaling (Rimmerman et al. 2011), coupled with the direct proven inhibitory action of CBD on inflammasomes (Huang et al. 2019) and downstream proteins, indicates the incomparable potential of CBD as an inflammasome-inhibitory drug target.

Evidence of an effect of CBD on inflammatory markers in humans is limited. A recent randomized controlled trial studied the effects of 12 weeks of 800 mg/day of pure CBD on inflammatory markers in 48 individuals with cocaine use disorder. It was seen that, compared to participants receiving placebo (n = 24), those participants treated with CBD (n = 24) had significantly lower levels of IL-6 ($p = 0.017$), vascular endothelial growth factor (VEGF; $p = 0.032$), intermediate monocytes CD14+CD16+ ($p = 0.024$), and natural killer CD56negCD16hi ($p = 0.000$).(Morissette et al. 2021) An earlier clinical study in patients with type 2 diabetes assessed CBD effects on three inflammatory

markers: IL-6, CRP, and tumor necrosis factor-α (TNF-α). The authors found no significant difference between the CBD (n = 13) and placebo (n = 14) groups on these markers with 100 mg CBD twice daily for 13 weeks; however, this dose is low compared to other human studies (Bergamaschi et al. 2011; Leweke et al. 2012; Morissette et al. 2021) that use higher doses of CBD (600 – 800 mg/day), which may explain lack of therapeutic effects seen with CBD in this study.(Jadoon, Tan, and O'Sullivan 2017)

Effects of CBD on models of CV inflammation including pericarditis:

CBD improves endothelial function, and endothelial dysfunction is an important therapeutic target in a number of 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 (Stanley et al. 2015; Saoirse E. O'Sullivan et al. 2009) 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-1β, IFN-gamma, 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 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) This 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.(Lozano et al. 2020) In conclusion, CBD administered by subcutaneous injection reduced a number of markers reflecting heart failure in this model system.

Cardiol Therapeutics is currently conducting a trial in patients with acute myocarditis (IND 145215). A trial in patients with COVID-19 at high CV risk (IND 152096) has been discontinued due to a lack of eligible hospitalized COVID-19 patients.

The efficacy of cannabidiol has been tested in a mouse model of acute pericarditis that was developed to investigate whether the pathophysiology of acute pericarditis is linked to a virus or another irritant activating the NLRP3 inflammasome, leading to IL-1β release, COX-2 activation, and prostaglandins production. (Mauro et al. 2021) The model uses zymosan A, a product of the yeast wall that activates NLRP3, injected directly into the pericardial space. Pericardial inflammation is measured by echocardiography (pericardial effusion) and at pathology (pericardial thickening, expression of the NLRP3 inflammasome component ASC). Results have demonstrated that cannabidiol treatment significantly reduces the pericardial effusion and pericardial thickening induced by zymosan A in this model.

Additional *in vitro* models using activated murine macrophages have demonstrated cannabidiol's ability to significantly inhibit release of the inflammatory cytokines IL-1β and IL-6, and significantly inhibit transcription of NLRP3 and pro-IL-1β. Together, these results suggest cannabidiol plays a role in attenuating multiple inflammatory pathways, including inhibiting activation of the NLRP3 inflammasome. These results have been presented at and the American Heart Association Scientific Sessions 2022. (Martinez-Naya 2022). This model has been used previously to demonstrate the efficacy of colchicine, IL-1 blockers anakinra and rilonacept, and NLRP3 inhibitors in reducing pericardial effusion and thickening. Cannabidiol has now also been shown to significantly reduce pericardial effusion and thickening in this mouse model of acute pericarditis, suggesting cannabidiol may represent a novel strategy for treating pericarditis, its complications, and preventing its recurrence.

Unmet need:

The recent US Database Study (A. Klein et al. 2021) found the most-commonly prescribed treatments for a first episode were colchicine alone (12%), or with NSAIDs (14%). Second, third, fourth, and fifth episodes were most-commonly treated with colchicine alone, corticosteroids alone, or another drug (not colchicine, corticosteroid, or NSAID; included intravenous immunoglobulin, azathioprine, methotrexate, and cyclosporine). The percentage of patients receiving something other than

corticosteroids, NSAIDs, or colchicine, alone or in combination, rose from 4% in the first episode up to 17% in the fourth episode and 15% in the fifth episode. This data was collected prior to the publication of the RHAPSODY trial and subsequent approval of rilonacept by the FDA for treatment of recurrent pericarditis and reduction in risk of recurrence.(A. L. Klein, Imazio, et al. 2021)

The low level of utilization of colchicine is likely due to a multitude of factors. Colchicine has a narrow therapeutic window with risk of fatal overdose, significant drug interactions, and neuromuscular toxicity. In addition, approximately 10% to 15% of patients experience significant gastrointestinal (GI) side effects with colchicine, including GI intolerance or severe diarrhea, requiring treatment discontinuation.(Cremer et al. 2016) Colchicine resistance likely leads to its use being abandoned in many patients.

The ESC guidelines stipulate that corticosteroids should be prescribed for the management of pericarditis episodes only in cases of incomplete response, intolerance, or contraindications to NSAIDs and colchicine because of their unfavorable long-term benefit-risk profile. Corticosteroid use is associated with side effects, including weight gain, diabetes, osteoporosis, avascular bone necrosis, and increased risk for infections.(Massimo Imazio et al. 2008) For the management of pericarditis, corticosteroids are usually administered at low to moderate doses and can provide rapid control of symptoms. However, they often require many months of tapering after the normalization of CRP levels. In addition, there is a high rate of pericarditis relapse when corticosteroid use is tapered or stopped (Maisch et al. 2004; Lotrionte et al. 2010), particularly in the absence of concurrent colchicine treatment.

Patients with recurrent pericarditis who are refractory or intolerant to current therapeutic management options or who require long-term administration of corticosteroids to control their disease can be particularly challenging to manage. While rilonacept is now available to some of these patients, its uptake has been low and there is the need for a safe, well tolerated, oral, accessible medication to add to the therapeutic options for these patients.

Rationale for pilot study:

This pilot study is to assess the tolerance and safety of CardiolRx™ during the resolution of pericarditis symptoms, evaluate improvement in objective measures of disease, and during the extension period assess the feasibility of weaning concomitant background therapy including corticosteroids while taking CardiolRx™. The results of this trial will inform the feasibility of designing a randomized double blind withdrawal trial to assess the effects of CardiolRx™ vs placebo in the treatment and prevention of recurrent pericarditis.

4 STUDY OBJECTIVES

4.1 Efficacy

4.1.1 Primary Objective

The primary objective is to evaluate the effect of treatment with CardiolRx™ on recurrent pericarditis.

4.1.2 Primary Efficacy Endpoint

The primary efficacy endpoint is patient-reported pericarditis pain using an 11-point NRS pain score, validated across multiple conditions with acute and chronic pain (Dworkin et al. 2005; Mannion et al. 2007; Hawker et al. 2011) from baseline (highest pain score within the past 7 days of Day 1) to Week 8 (highest pain score during the past 7 days of Week 8).

4.1.3 Additional Efficacy Parameters of Interest

- Pain score using 11-point NRS from baseline (highest pain score within the past 7 days of Day 1) to Week 26 (highest pain score during the past 7 days of Week 26)
- Percentage of patients with normalized CRP levels at 8 weeks (for patients with CRP ≥ 1.0 mg/dL at baseline)
- Percentage of patients with pericarditis recurrence during the EP
- Percentage of patients with normalized CRP levels at 26 weeks (for patients with CRP ≥1.0 mg/dL at baseline)
- Time to CRP normalization for patients with CRP ≥1.0 mg/dL at baseline
- CRP change from baseline at 26 weeks (%)

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 C-SSRS as well as changes in laboratory parameters, including liver function parameters and INR as well as ECG intervals and rhythm during the 26-week study period.

5 STUDY POPULATION

5.1 Enrolment and Study Centers

Approximately 25 patients will be enrolled in multiple centers.

5.2 Inclusion Criteria

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

1. Male or female 18 years of age or older
2. Diagnosis of at least two episodes of recurrent pericarditis*,
3. At least 1 day with pericarditis pain ≥4 on the 11-point NRS within prior 7 days
4. One of;
    a. CRP** level ≥1.0 mg/dL within prior 7 days **OR**
    b. Evidence of pericardial inflammation assessed by delayed pericardial hyperenhancement on CMR
5. Currently receiving NSAIDs and/or colchicine and/or corticosteroids for treatment of pericarditis (in any combination) in stable doses
6. Male patients 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.
7. 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 year absence of vaginal bleeding or spotting and confirmed by follicle stimulating hormone [FSH] ≥40 mIU/mL [or ≥ 40 IU/L] if less than 2 years postmenopausal) or be surgically sterile.

* Diagnosis of pericarditis according to the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al. 2015):

At least two of:

a. Pericarditic chest pain
b. Pericardial rub
c. New widespread ST-segment elevation or PR-segment depression according to ECG findings
d. Pericardial effusion (new or worsening)

** Conversion: 1 mg/dL CRP = 10 mg/L hs-CRP

5.3 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Diagnosis of pericarditis that is secondary to specific prohibited etiologies, including tuberculosis (TB); neoplastic, purulent, or radiation etiologies; post-thoracic blunt trauma (e.g., motor vehicle accident); myocarditis
2. Estimated glomerular filtration rate (eGFR) <30 mL/min
3. 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
4. Sepsis, defined as documented bacteremia at the time of screening or other documented active infection
5. Prior history of sustained ventricular arrhythmias
6. History of QT interval prolongation
7. QTc interval > 500 msec (please refer to Section 9.2.3 for bundle branch block, bifascicular block and paced rhythm correction)
8. Current participation in any research study involving investigational drugs or device
9. Inability or unwillingness to give informed consent
10. Ongoing drug or alcohol abuse
11. On any cannabinoid during the past month
12. Women who are pregnant or breastfeeding
13. Current diagnosis of cancer, with the exception of non-melanoma skin cancer
14. Any factor, which would make it unlikely that the patient can comply with the study procedures
15. Showing suicidal tendency as per the C-SSRS, administered at screening
16. On digoxin and/or type 1 or 3 antiarrhythmics
17. On immunosuppressive therapy with any of the following:
    a. Rilonacept
    b. Anakinra
    c. Canakinumab
    d. Methotrexate
    e. Azathioprine
    f. Cyclosporine
    g. IVIG

6 STUDY DESIGN

6.1 Summary of Study Design

Multi-center, open label Pilot Study.

Patients who present with recurrent pericarditis will be screened and informed consent obtained.

Baseline assessments include the following: Clinical assessment, including vital signs, pain score NRS, 12-lead ECG; C-SSRS as well as hematology and blood chemistry and a pregnancy test for women with child-bearing potential. If CRP was measured within 7 days of Day 1, this value will be used as the baseline value. If there is no CRP measurement available within 7 days of Day 1, CRP needs to be measured at baseline.

Concomitant medications are recorded and any (S)AEs after informed consent has been obtained.

Study treatment will be initiated in the evening of Day 1, after all baseline assessments are completed.

Oral administration (accompanied by food) is as follows:

- Initial starting dose (Day 1 p.m. dose to Day 3 a.m. dose):
  5 mg/kg of body weight CardiolRx™ b.i.d.
- Day 3 p.m. dose to Day 10 a.m. dose:
  7.5 mg/kg of body weight CardiolRx™ b.i.d.
- Day 10 p.m. dose to end of treatment period (a.m. dose at week 26):
  10.0 mg/kg of body weight CardiolRx™ b.i.d.
- The morning and evening doses should be taken minimally 6 hours and maximally 18 hours between each intake.

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 Extension Period

Unless contraindicated in the opinion of the investigator, after 8 weeks of study treatment, patients will enter an 18-week extension period (EP) in which they continue study treatment while their concomitant medications to treat pericarditis will be weaned, as described in Section 6.6.

6.3 Follow-up Procedures

At every assessment before study drug dose increase the patient will be re-evaluated. This includes 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, blood chemistry including liver function tests, hematology as well as INR assessments will be carried out at selected visits. Concurrent medications and (S)AEs will be recorded at all visits.

Final efficacy assessments will take place after 26 weeks of study treatment and include a clinical assessment, vital signs, Pain score NRS, a 12-lead ECG, the C-SSRS, as well as laboratory assessments.

For patients who do not enter the EP, final assessments will be done after 8 weeks, i.e. at Visit 5.

6.4 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.

6.5 Premature Interruption or Withdrawal from Study Treatment

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

6.5.1 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 9.2.11.3.
- Development of an AE or any medical condition, which, in the opinion of the investigator, necessitates permanent suspension of study treatment.
- If the patient did not tolerate the starting dose of 5 mg/kg of body weight b.i.d.
- 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 AEs should be reported, regardless of whether or not the event occurs under the care of another physician or institution.

6.5.2 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.

6.5.3 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.

6.6 Concomitant Treatments

Patients must be on SOC treatments for pericarditis with either NSAIDs, colchicine, or corticosteroids (in any combination) for at least 72 hours prior to Day 1. Unless contraindicated, these SOC treatments will be weaned during the 18 weeks EP as follows:

NSAIDs will be weaned within 2 weeks after the EP entry and corticosteroids within 6 weeks of EP entry (by 5 mg prednisone or equivalent every week).

For patients not taking corticosteroids, colchicine will be weaned between 2 and 4 weeks of EP entry, and for those on corticosteroids, colchicine weaning will be between 6 and 8 weeks of EP entry. Should it become evident that weaning of colchicine leads to high levels of pericarditis recurrence, the study leadership and the sponsor may decide colchicine weaning will no longer be performed during the EP.

Patients will not be allowed to be on immunosuppressive therapy with rilonacept, anakinra, canakinumab, methotrexate, azathioprine, cyclosporine, mycophenolate and/or IVIG and cannot take any cannabinoids during the study period nor strong inducers of CYP3A4 and CYP2C19 (see Section 17.7).

Use of digoxin and/or type 1 or 3 antiarrhythmics is an exclusion criterion for the trial. No drugs that are known to prolong QTc intervals should be started during the study (Appendix 17.6).

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 17.8.

6.7 Management of Pericarditis Recurrence During the Extension Period

Pericarditis recurrence during the extension period is defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis in the opinion of the investigator. At any timepoint during the EP, patients who experience suspected recurrence of their pericarditis will have been instructed to inform their site Investigator as soon as possible. Patients who experience a suspected recurrence of pericarditis symptoms will be requested to report to the study site/clinic for a scheduled or unscheduled visit, during which clinical assessments will be performed to gather all the necessary diagnostic data to confirm or rule out the presence of pericarditis recurrence. The Investigator will evaluate all assessments performed for a diagnostic workup, whether at the study site or at locations outside.

Following communication with the study medical monitor, patients who report at least 1 day with pericarditis pain measurement ≥4 on the 11-point NRS **AND** have a CRP value ≥1 mg/dL (either on the same day or separated by no more than 7 days) during the EP of the trial will receive rescue therapy at the discretion of the investigator, i.e., if not already taking; analgesics first, then NSAIDs, and then colchicine. Immunosuppressive therapy such as corticosteroids or rilonacept may be added for pericarditis recurrence at the discretion of the investigator.

6.8 Coronavirus 2019 (COVID-19) Measures

The study will be initiated while the COVID-19 pandemic is ongoing. Testing for SARS-CoV-2 is not required for this study and Investigators should follow local guidance. Should a study participant become infected with SARS-CoV-2 / contract or become suspected to have contracted COVID-19, standards for testing and management should be followed according to local and site-specific guidelines.

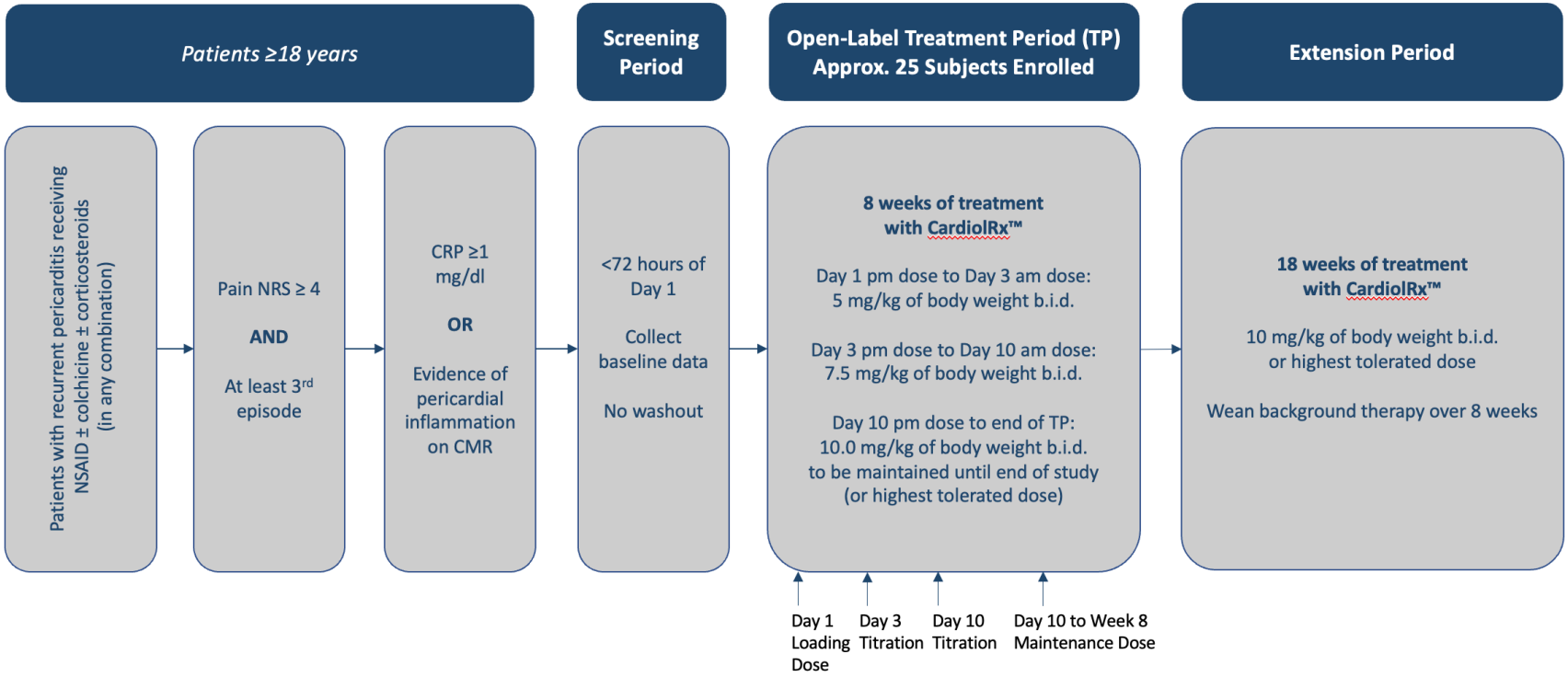
SARS-CoV-2 infection (if asymptomatic), COVID-19 (including pneumonia related to COVID-19), and COVID-19-related symptoms, will be reported as adverse events.

Treatments used for COVID-19 as well as vaccines are allowed without restriction during the study. They will be reported in the eCRF in the same way as any other concomitant medications described in Section 6.6 of the protocol.

The study design minimizes the physical contacts and therefore the associated risks of infection by the SARS-CoV-2. The scheduled study follow-up contacts will be performed as virtual visits and resupply of study treatment may be performed via shipment to

patient’s home, when locally allowed and if feasible. The only mandatory hospital visits are those where laboratory tests for safety are required per protocol.

7 STUDY PLAN


Patients ≥18 years
Screening Period
Open-Label Treatment Period (TP)
Approx. 25 Subjects Enrolled
Extension Period
Patients with recurrent pericarditis receiving NSAID ± colchicine ± corticosteroids (in any combination)
Pain NRS ≥ 4
AND
At least 3rd episode
CRP ≥1 mg/dl
OR
Evidence of pericardial inflammation on CMR
<72 hours of Day 1
Collect baseline data
No washout
8 weeks of treatment with CardiolRx™
Day 1 pm dose to Day 3 am dose: 5 mg/kg of body weight b.i.d.
Day 3 pm dose to Day 10 am dose: 7.5 mg/kg of body weight b.i.d.
Day 10 pm dose to end of TP: 10.0 mg/kg of body weight b.i.d. to be maintained until end of study (or highest tolerated dose)
18 weeks of treatment with CardiolRx™
10 mg/kg of body weight b.i.d. or highest tolerated dose
Wean background therapy over 8 weeks
Day 1 Loading Dose
Day 3 Titration
Day 10 Titration
Day 10 to Week 8 Maintenance Dose

8 INVESTIGATIONAL PRODUCTS, DOSE AND DURATION OF TREATMENT

8.1 Investigational Product

CardiolRx™ is synthetically produced. It contains cannabidiol oil in a concentration of 100 mg/mL and is free of 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:

- Initial starting dose (Day 1 p.m. dose to Day 3 a.m. dose):
  5 mg/kg of body weight CardiolRx™ b.i.d.
- Day 3 p.m. dose to Day 10 a.m. dose:
  7.5 mg/kg of body weight CardiolRx™ b.i.d.
- Day 10 p.m. dose to end of study (a.m. dose at Week 26):
  10.0 mg/kg of body weight CardiolRx™ b.i.d.
- The morning and evening doses should be taken minimally 6 hours and maximally 18 hours between each intake.

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 study (26 weeks post start of study medication).

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 supplied for each assessment period.

8.4.2 Labelling and Storage

All investigational drugs will be labeled in English and Spanish according to local regulations for investigational drugs.

All clinical drug supplies are to be stored in a secure, limited-access area as follows:

- Room temperature 59ºF - 86ºF or refrigerated 36ºF - 47ºF
- The study supplies need to be protected from light (to be kept in closed cartons or boxes).
- The study supplies need to be stored in an upright position to prevent leakage.

9 CONDUCT OF THE STUDY

9.1 Scheduling of Study Procedures

Patients diagnosed with recurrent pericarditis will be invited to participate in the study. Informed consent must be obtained PRIOR to performing any study-related procedure. There is no time limit between obtaining informed consent and assigning study treatment to the patient. Some of the scheduled follow-up visits may be performed remotely if it's not possible to conduct an in-patient visit. The following must be in place to enable a remote visit to take place:

- The patient is able to obtain an ECG recording, which can immediately be transmitted to the study site
- The patient agrees to go to a local laboratory to have the blood tests planned by protocol performed

Visit 1 (Screening and baseline assessments – within 72 hours of Day 1)
The following evaluations will be performed a baseline:

- Written informed consent
- Demographics
- Medical History/Current conditions, including prior CV events and interventions
- Clinical assessment
- Vital signs, including heart rate (HR), blood pressure, body height and weight
- Collect highest NRS pain score within the past 7 days of DAY 1
- 12-lead ECG
- C-SSRS
- Collection of concurrent medication and medication history for the previous 1 month
- Local laboratory assessments, including CRP*, CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR, pregnancy test (in women with childbearing potential)
- AE and SAE recording after informed consent has been obtained
- Assign study treatment to the patient

* only if no measurement within 7 days of Day 1 is available

Start of study medication in the evening of Day 1.

Visit 2 (Day 3 + 2 days) – This visit may be performed as a virtual visit if an in-person visit is not possible as long as the ECG recording can be obtained
The following evaluations will be performed on Day 3 after start of study medication:

- Vital signs, including HR and blood pressure (if visit in person)
- Review/collection of daily diary NRS pain scores, if not submitted electronically to Patient Portal if the patient has completed the questionnaire on paper

- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours); QTc intervals on ECG to be reviewed by site investigator, or designate, who decides if patient can continue study medication. If the visit is done remotely, the patient will record the ECG on a portable device at home or will have the ECG recording performed at a local clinic. The tracings must immediately be transmitted to the site for review.
- Study drug dose increase to 7.5 mg/kg of body weight b.i.d. if patient tolerating starting dose of 5 mg/kg of body weight b.i.d. (If patient did not tolerate the starting dose of 5 mg/kg of body weight b.i.d., the patient will stop the study medication but will continue in the study and follow all assessments until Visit 5 to be included in the safety analyses)
- Study drug accountability
- Recording of changes in concomitant medications
- AE and SAE recording

Visit 3 (Day 10 ± 2 days) – This visit may be performed as a virtual visit if an in-person visit is not possible as long as the ECG recording can be obtained

The following evaluations will be performed on Day 10 after start of study medication:

- Vital signs, including HR and blood pressure (if visit in person)
- Review/collection of daily diary NRS pain scores, if not submitted electronically to Patient Portal if the patient has completed the questionnaire on paper
- Collect highest NRS pain score within the past 7 days
- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours); QTc intervals on ECG to be reviewed by site investigator, or designate, who decides if patient can continue study medication. If the visit is done remotely, the patient will record the ECG on a portable device at home or will have the ECG recording performed at a local clinic. The tracings must immediately be transmitted to the site for review.
- Study drug dose increase to 10 mg/kg of body weight b.i.d. if patient tolerating 7.5 mg/kg of body weight b.i.d. If patient did not tolerate 7.5 mg/kg of body weight b.i.d., patient can return to 5 mg/kg of body weight b.i.d.
- Study drug accountability
- Recording of changes in concomitant medications
- AE and SAE recording

Visit 4 (Week 3 ± 3 days) – This visit may be performed as a virtual visit if an in-person visit is not possible as long as the ECG recording can be obtained and the laboratory assessments can be done by a local laboratory.

The following evaluations will be performed at 2 weeks after start of study medication:

- Clinical assessment (if visit in person)
- Vital signs, including HR and blood pressure (if visit in person)
- Review/collection of daily diary NRS pain scores, if not submitted electronically to Patient Portal if the patient has completed the questionnaire on paper

- Collect highest NRS pain score within the past 7 days
- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours); QTc intervals on ECG to be reviewed by site investigator, or designate, who decides if patient can continue study medication. If the visit is done remotely, the patient will record the ECG on a portable device at home or will have the ECG recording performed at a local clinic. The tracings must immediately be transmitted to the site for review.
- Study drug dose adjustment (if patient did not tolerate 10 mg/kg of body weight b.i.d., patient can return to 7.5 mg/kg of body weight b.i.d.
- Study drug accountability
- Recording of changes in concomitant medications
- AE and SAE recording
- Local laboratory assessments, including CRP, CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR (if visit not in person, patient needs to go to a local laboratory for blood collection and assessments)

Visit 5 (Week 8 ± 4 days) – final study visits for patients not continuing in the EP

The following evaluations will be performed at 8 weeks after start of study medication:

- Clinical assessment
- Vital signs, including HR, blood pressure and body weight
- Review/collection of daily diary NRS pain scores, if not submitted electronically to Patient Portal if the patient has completed the questionnaire on paper
- Collect highest NRS pain score within the past 7 days
- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours); QTc intervals on ECG to be reviewed by site investigator, or designate, who decides if patient can continue study medication
- C-SSRS
- Study drug accountability
- Recording of changes in concomitant medications
- Start weaning background therapy over the next 8 weeks for patients continuing in the EP
- AE and SAE recording
- Local laboratory assessments, including CRP, CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR

Visit 6 (Week 12 ± 4 days) – Virtual visit

The following evaluations will be performed virtually at 12 weeks after start of study medication:

- Review/collection of daily diary NRS pain scores, if not submitted electronically to Patient Portal
- Collect highest NRS pain score within the past 7 days
- Study drug accountability
- Recording of changes in concomitant medications
- AE and SAE recording

Visit 7 (Week 16 ± 4 days)
The following evaluations will be performed at 16 weeks after start of study medication:

- Clinical assessment
- Vital signs, including HR and blood pressure
- Review/collection of daily diary NRS pain scores, if not submitted electronically to Patient Portal if the patient has completed the questionnaire on paper
- Collect highest NRS pain score within the past 7 days
- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours); QTc intervals on ECG to be reviewed by site investigator, or designate, who decides if patient can continue study medication
- Study drug accountability
- Recording of changes in concomitant medications
- AE and SAE recording
- Local laboratory assessments, including CRP, CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR

Visit 8 (Week 20 ± 5 days) – Virtual visit
The following evaluations will be performed virtually at 20 weeks after start of study medication:

- Review/collection of daily diary NRS pain scores, if not submitted electronically to Patient Portal if the patient has completed the questionnaire on paper
- Collect highest NRS pain score within the past 7 days
- Study drug accountability
- Recording of changes in concomitant medications
- AE and SAE recording

Visit 9 (Week 26 ± 5 days)
The following evaluations will be performed at 26 weeks after start of study medication:

- Clinical assessment
- Vital signs, including HR, blood pressure and body weight
- Review/collection of daily diary NRS pain scores, if not submitted electronically to Patient Portal if the patient has completed the questionnaire on paper
- Collect highest NRS pain score within the past 7 days
- 12-lead ECG 5 hours post morning dose (time window 3.5 – 6 hours)
- C-SSRS
- Study drug accountability
- Recording of changes in concomitant medications
- AE and SAE recording
- Local laboratory assessments, including CRP, CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR

If a visit is missed and/or an ECG cannot be performed, the patient should stay on the current study drug dose until the next assessment.

9.2 Clinical Procedures and Safety Evaluations

9.2.1 Informed Consent

Patients who comply with 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. 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 collection of age, sex and race.

9.2.3 Standard 12-lead Electrocardiogram (ECG)

A 12-lead ECG will be performed at baseline, and at all in-person follow-up visits. Visits 2 (Day 3), 3 (Day 10) and 4 (Week 3) can only be virtual if an ECG can be performed and transmitted to the site for review.

The ECG after start of study medication will be recorded 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. Continuation on study drug will be assessed by the investigator or designate dependent on interrogation of the ECG, most importantly the QT interval.

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 ($QT_C = QT / \sqrt{RR}$) or Fridericia's formula ($QT_C = QT / RR^{1/3}$) to create the QTc interval. Each patient should have the QTc measured using the same method on all designated days in the study.

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)

Similarly, ventricular paced rhythm with an increased QRS duration can impact the QT interval. In patients with ventricular paced rhythm, 50ms should be subtracted from the Bazett's formula or Fridericia's formula.(Chakravarty et al. 2015)

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 new 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 medications taken in the past month.

9.2.5 Clinical Assessment

A routine clinical assessment is required at baseline, and at all in-person visits. Any abnormality must be recorded.

9.2.6 Vital Signs, Body Height and Weight

Vital signs including blood pressure, HR and body weight will be recorded at baseline (Visit 1), and at all in-person visits. Body height will be recorded at baseline (Visit 1).

9.2.7 Collection of NRS Scores

Patients will be asked to enter their pain scores into a diary on a daily basis using the 11-point NRS. Patients will have the choice to complete the NRS scale either on paper or in an electronic patient reported outcomes platform – i.e., eSOCDAT Patient Portal. Access to the eSOCDAT Patient Portal is restricted to authorized users only. State-of-the-art procedures are in place to prevent unauthorized access and data corruption, namely, firewalls, up-to-date virus scanning in addition to the encryption of data stored in the database and transmitted via the Internet. Patients will be provided with a unique username and password to access the eSOCDAT Portal.

In addition, the highest NRS pain score within the past 7 days will be recorded at baseline (patient recall) and at each visit after randomization from the Patient Portal entries/diaries or, if not available, from patient recall.

9.2.8 Concomitant Treatment

Guidelines for concomitant treatment are given in Section 6.6 of this protocol.

All changes in concomitant medications during the study must be recorded, as must those started within one week of study entry and continued thereafter.

9.2.9 Laboratory Tests

Laboratory tests include CRP, CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR, pregnancy test (female patients of childbearing potential only). Please see Appendix 17.2 for the exact schedule of all laboratory tests. Visit 4 (Week 3) can only be virtual if the laboratory assessments can be performed by a local laboratory.

9.2.10 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, patients will undergo C-SSRS evaluations at baseline, at Week 8 and at Week 26.

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

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

9.2.11 Management of AEs

9.2.11.1 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 patient 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.

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

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

1. Death

2. Life-threatening situation (patient was at risk of death at the time of the event. This does not refer to an event that might have caused death if it was of greater intensity.)
3. New in-patient hospitalization or prolongation of existing index hospitalization
4. Persistent or significant disability or incapacity
5. Congenital anomaly or birth defect
6. QTc interval increases to > 500 msec or >60 msec from baseline.
7. 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 9.2.11.3 for the definition of potential DILI.)

All SAEs experienced by a patient after informed consent has been obtained must be reported to SOCAR Research (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 S*AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology.*

Pre-existing conditions should be recorded upon patient enrolment (including start date of the condition, and severity - mild, moderate, severe). After the patient signs the informed consent form, any worsening of these conditions would be recorded.

Any new conditions would be recorded including date of onset, date of resolution, severity (mild, moderate, severe, or serious as defined above) and possible relationship to study drug or procedure. As part of the source notes, follow up clinical assessments, laboratory tests, ECGs and diagnostic imaging related to AE should be documented.

9.2.11.2 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.

9.2.11.3 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.

9.2.11.4 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.

9.2.11.5 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.

Drugs that are known to prolong QTc intervals must not be started during the study (Appendix 17.6).

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 17.8).

9.2.12 Drug Accountability

Drug accountability will be performed at all visits after randomization and start of study medication, including virtual visits.

10 CRITERIA FOR EVALUATION OF STUDY RESULTS

10.1 Criteria for Evaluation of Efficacy

10.1.1 Primary Efficacy Outcome

The primary efficacy endpoint of this Pilot study is the change in patient-reported pericarditis pain using an 11-point NRS from baseline (highest score within the past seven days of Day 1) to Week 8 (highest score recorded within the past seven days).

10.1.2 Additional Efficacy Parameters of Interest

Additional efficacy parameters of interest are listed in Section 4.1.3.

10.2 Criteria for Evaluation of Safety

The safety parameters are listed in Section 4.2.2.

10.3 Description of Patient Groups for Analyses

10.3.1 Population for Efficacy and Safety Analyses

All patients who were enrolled and took at least one dose of study medication will be included in the safety analyses.

Patients who do not tolerate the initial dose of 5 mg/kg of body weight b.i.d. will stay in the study for safety evaluations but will be replaced for the assessment of efficacy.

11 STATISTICAL METHODS

11.1 Sample Size Estimation

No formal sample size was calculated for this Pilot study. Approximately 25 patients will be included in this study. Patients who do not tolerate the initial dose of 5 mg/kg of body weight b.i.d. will stay in the study for safety evaluations but will be replaced for the assessment of efficacy.

11.2 Outcome Analyses

Given the small sample size and the design of the study (no placebo comparison), no inferential statistical analyses are planned.

Depending on their distribution, continuous variables will be expressed as mean ± standard deviation (SD) or as median (interquartile range [IQR]). Categorical variables will be expressed in counts with percentages.

For all continuous variables, including the NRS pain scores, the change from baseline will be presented as summary statistics.

For categorical variables, summary statistics will be calculated.

11.3 Safety Analyses

The same approaches as in Section 11.2 will be taken.

11.4 Missing Values

All attempts will be made to minimize missing follow-up data. No imputations for missing data are planned.

11.5 Stopping Guidelines

If, after at least 12 patients have been enrolled, more than 50% of patients are suffering from pericarditis recurrences, the study will be stopped.

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)

OZMOSIS Inc will be responsible for site management and site monitoring which includes site initiation, site training, remote/in-person site visits and close out visits. SOCAR will be responsible for overall study management, including build of the eCRFs, data management, oversight of the electronic trial master file (eTMF) and statistical analysis. TMC Pharma is responsible for pharmaco-vigilance.

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.

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

Ozmosis is responsible for monitoring according to applicable 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/inspections. 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 English and the local language(s) 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, including final study drug accountability, 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 9.2.11.1 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, IRB/ERB 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.

15 STUDY TIMELINES

Eligible patients will be enrolled and will be followed for 26 weeks. We estimate the following: 4 months for site setup, a recruitment period of 12 months, time for data collection, cleaning and database lock 2 months, analysis and reporting 2 months, resulting in a total study time of approximately 26 months.

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17 APPENDICES

17.1 Declaration of Helsinki

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

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the

52nd WMA General Assembly, Edinburgh, Scotland, October 2000
and the
Washington DC 2002 clarification on Paragraph 29

A. INTRODUCTION

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

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

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

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

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

investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

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

available, Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

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

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

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

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

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

17.2 Schedule of Study Procedures

VISIT	1	2	3		4		5	6	7	8	9
DAYS	Within 72 hours of Day 1	3	10								
WEEKS					3		8[8,9]	12	16	20	26
		Virtual visit if feasible and not possible in person	Virtual visit if feasible and not possible in person		Virtual visit if feasible and not possible in person			Virtual visit		Virtual visit	
Informed Consent	X										
Demographics	X										
Medical History	X										
Clinical assessment	X						X		X		X
Vital signs[1]	X	X	X		X		X		X		X
Highest NRS pain score within the past 7 days recorded[11]	X		X		X		X	X	X	X	X
Review/Collection of NRS Pain Scores		X	X		X		X	X	X	X	X
12-lead ECG[2]	X	X	X		X		X		X		X
C-SSRS	X						X				X
Study medication[3]	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX										
Start of EP (weaning of concomitant Rx)							X				
Study Rx adjustment and accountability[4]		X	X		X		X	X	X	X	X
Concomitant medication recording	X	X	X		X		X	X	X	X	X
AE and SAE recording[5]	X	X	X		X		X	X	X	X	X
Laboratory	DAYS			WEEKS							
Local Laboratory	1[6]	3	10		3		8	12	16	20	26
CRP[10]	X				X		X		X		X
CBC	X				X		X		X		X
ALT/AST	X				X		X		X		X
Alkaline Phosphatase	X				X		X		X		X
Bilirubin	X				X		X		X		X
Creatinine/ eGFR	X				X		X		X		X
INR	X				X		X		X		X
Pregnancy Test[7]	X										

[1] Vital signs include heart rate and blood pressure; body weight at baseline, at all in-person visits; height at baseline
[2] Except for Visit 1, all ECGs to be recorded 3.5 – 6 hours post morning dose of study Rx
[3] Start of study drug in the evening of Day 1 after completion of baseline assessments
[4] Study drug adjustment up to Visit 4 (Week 3); drug accountability at all visits, including virtual visits
[5] Adverse Event recording starts after informed consent is obtained
[6] All local laboratory assessments at baseline to be performed before start of study Rx
[7] Pregnancy test in women with childbearing potential
[8] For patients not able to participate in the EP, Visit 5 (Week 8) is the end of study visit
[9] EP starting after Visit 5 until Visit 9
[10] If CRP was measured within 7 days of Day 1, this value will be used as the baseline value. If there is no CRP measurement available within 7 days of Day 1, CRP needs to be measured at baseline.
[11] Highest NRS pain score within the past 7 days of Day 1 from patient recall; after randomization from the Patient Portal entries/diary entries or, if not available, from patient recall
[12] Visits 2 (Day 3), 3 (Day 10), and 4 (Week 3) can be performed virtually, via video link, if an ECG can be performed with direct transmission to site for review by investigator or designate and local laboratory assessments at Visit 4 can be arranged

17.3 Numerical Rating Scale (NRS)

Patients will be asked to select the score that best describes their average level of pericarditis pain over the previous 24 hours using this 11-point NRS, where zero (0) indicates ‘no pain’ and ten (10) indicates ‘pain as bad as it could be’.

0	1	2	3	4	5	6	7	8	9	10

On this scale of 0 – 10, zero (0) indicates ‘no pain’ and ten (10) indicates ‘pain as bad as it could be’, please rate your pericarditis pain on average over the last 24 hours. Please tick or circle only one number.

Patients will have the choice to complete the NRS scale either on paper or in an electronic patient reported outcomes platform – i.e. eSOCDAT Patient Portal. Access to the eSOCDAT Patient Portal is restricted to authorized users only. State-of-the-art procedures are in place to prevent unauthorized access and data corruption, namely, firewalls, up-to-date virus scanning in addition to the encryption of data stored in the database and transmitted via the Internet. Patients will be provided with a unique user name and password to access the eSOCDAT Portal.

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version
Version 1/14/09

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

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

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

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

PART 1 OF 5

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

☐ Section below not applicable

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

PART 2 OF 5

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

PART 3 OF 5

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

PART 4 OF 5

☐ Section below not applicable

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

Following must be answered

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

PART 5 OF 5

☐ Section below not applicable

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

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit
Version 1/14/09

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

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

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

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

PART 1 OF 5

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

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

PART 2 OF 5

☐ Section below not applicable

INTENSITY OF IDEATION

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

Most Severe Ideation: _____

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

PART 3 OF 5

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

PART 4 OF 5

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

Following must be answered

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

PART 5 OF 5

☐ Section below not applicable

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

17.6 Drugs that can prolong QTc intervals

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

CredibleMeds® 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)	Hysinglaâ,¢ ER and others
Hydroquinidine (Dihydroquinidine) (KR)	Serecor
Hydroxychloroquine (KR)	Plaquenil and others
Hydroxyzine (CR)	Atarax and others
Ibogaine (KR)	
Ibutilide (KR)	Corvert
Iloperidone (PR)	Fanapt and others
Imipramine (Melipramine) (PR)	Tofranil
Indapamide (CR)	Lozol and others
Inotuzumab ozogamicin (PR)	Besponsa
Isradipine (PR)	Dynacirc
Itraconazole (CR)	Sporanox and others
Ivabradine (CR)	Procoralan and others
Ivosidenib (PR)	Tibsovo
Ketanserin (PR)	Sufrexal
Ketoconazole (CR)	Nizoral and others
Lacidipine (PR)	Lacipil and others
Lansoprazole (CR)	Prevacid and others

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

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

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

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

N[illegible] on this list are reviewed on an ongoing basis to assure [illegible] evidence [illegible] continued placement [illegible], this list changes regularly, we re[illegible]rg 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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17.7 Drugs That Are Strong Inducers of CYP3A4 and CYP2C19

17.7.1 CYP3A4 Inducers

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

17.7.2 CYP2C19 Inducers

- Rifampin

17.8 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 17.7.
4. Drugs listed in the table are arranged as follows: cardiovascular drugs, diabetes care drugs and then other commonly used drugs (in alphabetical order). The CYP or UGT isoform for which the drugs serve as a substrate are listed in the final column.
5. Many drugs serve as a substrate for more than one CYP or UGT isoform. They have only been recorded once in the table.
6. 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
			CYP2C9

Anti-diarrheal	Loperamide	May cause dehydration, weakness, faintness, rapid heart rhythm – discontinue if possible	CYP2C8
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 irritation and bleeding and increase action of warfarin anti-coagulants – change to other anti-inflammatory	CYP2C9
	Indomethacin	Can cause edema, increased potassium, sodium, creatinine and hypertension – adjust dose or change medication	CYP2C19
Antipsychotic	Clozapine	May cause low WBC, drowsiness, increased salivation, hypotension, blurred vision, seizures and cardiac inflammation (myocarditis) – monitor WBC, ECG – reduce dose or chose another agent	CYP2C8
	Haloperidol	QT prolongation, tardive dyskinesia – adjust dose or use different medication	CYP2C9
Anti-viral	Remdesivir	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	CYP2C8

		thoughts – reduce dose/change medication	
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 – adjust dose or d/c	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