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Cardiol Therapeutics Announces Study Results Demonstrating Protective Effects of CardiolRx™ in a Model of Acute Pericarditis

**Results Demonstrate Significant Reduction in Pericardial Effusion and Thickness
and Significant Suppression of Key Inflammatory Markers IL-1 β and IL-6**

Data Presented at The American Heart Association Scientific Sessions 2022

Oakville, ON – November 7, 2022 – Cardiol Therapeutics Inc. (**NASDAQ: CRDL**) (**TSX: CRDL**) (“**Cardiol**” or the “**Company**”), a clinical-stage life sciences company focused on the research and clinical development of anti-inflammatory and anti-fibrotic therapies for the treatment of heart diseases, announced today study results demonstrating that pharmaceutically manufactured cannabidiol (the active pharmaceutical ingredient in CardiolRx™) significantly reduces pericardial effusion and thickening in a pre-clinical model of acute pericarditis and significantly suppresses the secretion of key inflammatory markers interleukin-1 β (“IL-1 β ”) and interleukin-6 (“IL-6”) *in vitro*. The data were presented by Cardiol’s research collaborators from Virginia Commonwealth University (“VCU”) at The American Heart Association Scientific Sessions 2022 (“AHA2022”).

The poster entitled “Protective Effects of Pharmaceutically Manufactured Cannabidiol in a Mouse Model of Acute Pericarditis” was presented on November 5th within the “Late-Breaking Basic Science Posters” session of AHA2022. The authors concluded that the pharmaceutically manufactured cannabidiol administered in the study may represent a novel therapy for treating pericarditis and preventing its complications and recurrence. Data presented also demonstrated a dose-response effect on IL-1 β *in vitro*. In addition, cannabidiol was shown *in vitro* to significantly inhibit the transcription of IL-1 β and NLRP3, as measured by mRNA expression. NLRP3 is a sensor protein that comprises a part of the NLRP3 inflammasome, a large multiprotein complex that regulates inflammatory responses of the innate immune system. Cardiol has filed comprehensive patent applications with the U.S. patent office in connection with these new findings.

“The data presented at the AHA2022 by our research collaborators from VCU provides additional rationale for our recent decision to prioritize our Phase II pilot study in patients with recurrent pericarditis and offers new insight into the molecular targets and mechanism of action of CardiolRx™,” commented Dr. Andrew Hamer, Cardiol Therapeutics’ Chief Medical Officer and Head of Research & Development. “Pericarditis results from inflammation of the pericardium, the sac that surrounds the heart, and is manifested clinically by chest pain and by imaging signs of pericardial effusion and thickening. Significant accumulation of pericardial fluid and scarring can progress to life-threatening constriction of the heart. It is recognized that

pericarditis is associated with aberrant inflammasome activation, an intracellular process leading to the release of pro-inflammatory cytokines, including IL-1 β . The results presented over the weekend provide evidence that CardiolRx™ inhibits activation of the inflammasome pathway and other associated pro-inflammatory pathways. The magnitude of effect on multiple parameters as reported in the poster was notable and provides a strong scientific basis for investigating CardiolRx™ as a potential novel therapy in pericarditis care.”

The Company’s Phase II pilot study in recurrent pericarditis is expected to enroll 25 patients at major clinical centers in the United States specializing in pericarditis. The protocol has been designed in collaboration with thought leaders in pericardial disease. The study Chairman is Allan L. Klein, MD, Director of the Center of Pericardial Diseases and Professor of Medicine, Heart and Vascular Institute, at the Cleveland Clinic. The primary efficacy endpoint is the change, from baseline to 8 weeks, in patient-reported pericarditis pain using an 11-point numeric rating scale (“NRS”). The NRS is a validated clinical tool employed across multiple conditions with acute and chronic pain, including previous studies of recurrent pericarditis. Secondary endpoints include the pain score after 26 weeks of treatment, and changes in circulating levels of C-reactive protein, a commonly used clinical marker of inflammation.

In the pre-clinical *in vivo* study, acute pericarditis was induced by injecting Zymosan A, which activates NLRP3, into the pericardial sac thereby leading to the classical features of the inflamed pericardium: increased pericardial effusion and pericardial thickening; an accepted model of acute pericarditis. Groups were randomized to either receive intraperitoneal injections of cannabidiol, or an equal volume of vehicle control, administered following recovery from surgery. Pericarditis severity was assessed by the presence of effusion via echocardiography (measured as width of pericardial space) and pericardial thickening. Seven days after surgery the cannabidiol treated group had significantly reduced pericardial effusion (0.12 vs 0.26 mm, $p < 0.01$) and pericardial thickness (3.6 vs 6.5 μm , $p < 0.05$) when compared to the untreated control group.

In separate *in vitro* experiments, immune cells (J774.1 macrophages) were stimulated with lipopolysaccharide (“LPS”), adenosine triphosphate (“ATP”), or LPS+ATP, with or without cannabidiol. LPS+ATP induces IL-1 β secretion via NLRP3 inflammasome activation. Inflammatory cytokines IL-1 β and IL-6 were measured by ELISA. The LPS+ATP combination increased IL-1 β concentration vs control (449.1 vs 6.4 pg/ml, $p < 0.0001$); however, addition of cannabidiol treatment significantly reduced IL-1 β concentration (118.7 pg/ml, $p < 0.0001$ vs. LPS+ATP). Furthermore, a dose-response reduction in IL-1 β was observed with additional concentrations of cannabidiol. Separately, LPS alone was shown to significantly increase IL-6 concentration and that effect was abolished with cannabidiol treatment. LPS-induced IL-6 release is independent of NLRP3 activation, and the results suggest the effect of cannabidiol is not limited solely to the NLRP3 inflammasome pathway. Finally, gene expression using real-time polymerase chain reaction was performed for IL-1 β and NLRP3 messenger RNA following LPS administration to J774.1 macrophages. LPS was shown to significantly increase the transcription of NLRP3 and IL-1 β , but treatment with cannabidiol significantly reduced the level of transcription of both.

About The American Heart Association Scientific Sessions

Founded in 1924, the American Heart Association (“AHA”) is the oldest and largest voluntary organization dedicated to fighting heart disease and stroke. The AHA is a multidisciplinary organization who has invested more than \$5 billion in research, making it the largest not-for-profit funding source for cardiovascular and cerebrovascular disease research next to the

United States government. The AHA Scientific Sessions is an annual meeting that brings together academics, researchers, health care professionals, and industry to share the latest discoveries and biggest breakthroughs in cardiovascular science. Programming covers basic, clinical, and population science and is presented by global thought leaders.

About Recurrent Pericarditis

Recurrent pericarditis refers to inflammation of the pericardium (the membrane or sac that surrounds the heart) that follows an initial episode (frequently resulting from a viral infection). Patients may have multiple recurrences. Symptoms include debilitating chest pain, shortness of breath, and fatigue, resulting in physical limitations, reduced quality of life, emergency department visits, and hospitalizations. The only FDA-approved therapy for recurrent pericarditis, launched in 2021, is extraordinarily costly and is primarily used as a third-line intervention. The number of cases of patients seeking and receiving treatment for recurrent pericarditis annually in the U.S. is estimated at 38,000. Hospitalization due to recurrent pericarditis is often associated with a 6-8-day length of stay and cost per stay is estimated to range between \$20,000 and \$30,000 in the U.S.

About Inflammasomes

Inflammasomes are large multiprotein complexes which under normal conditions play an essential role in innate immunity and maintaining homeostasis. The inflammasome becomes abnormally activated under various conditions such as obesity, hypertension, diabetes, and autoimmunity. In the case of pericarditis, a trigger such as a virus may activate the inflammasome and elicit an inflammatory response through the release of pro-inflammatory cytokines such as IL-1 β , thereby leading to the pericardial effusion and thickness characteristic of the disorder.

About Cardiol Therapeutics

Cardiol Therapeutics Inc. (NASDAQ: CRDL) (TSX: CRDL) is a clinical-stage life sciences company focused on the research and clinical development of anti-inflammatory and anti-fibrotic therapies for the treatment of heart diseases. The Company's lead product candidate, CardiolRx™, is a pharmaceutically manufactured oral cannabidiol formulation that is being clinically developed for use in heart diseases. It is recognized that cannabidiol inhibits activation of the inflammasome pathway, an intracellular process known to play an important role in the inflammation and fibrosis associated with myocarditis, pericarditis, and heart failure.

Cardiol has received Investigational New Drug Application authorization from the United States Food and Drug Administration to conduct clinical studies to evaluate the efficacy and safety of CardiolRx™ in two diseases affecting the heart: (i) a Phase II multi-national, randomized, double-blind, placebo-controlled trial (the "ARCHER" trial) in acute myocarditis, an important cause of acute and fulminant heart failure in young adults and a leading cause of sudden cardiac death in people less than 35 years of age; and (ii) a Phase II multi-center open-label pilot study in recurrent pericarditis (inflammation of the pericardium), which is associated with symptoms including debilitating chest pain, shortness of breath, and fatigue, and results in physical limitations, reduced quality of life, emergency department visits, and hospitalizations.

Cardiol is also developing a novel subcutaneously administered drug formulation of cannabidiol intended for use in heart failure – a leading cause of death and hospitalization in the developed world, with associated healthcare costs in the United States exceeding \$30 billion annually.

For more information about Cardiol Therapeutics, please visit cardiolrx.com.

Cautionary statement regarding forward-looking information:

This news release contains “forward-looking information” within the meaning of applicable securities laws. All statements, other than statements of historical fact, that address activities, events, or developments that Cardiol believes, expects, or anticipates will, may, could, or might occur in the future are “forward-looking information”. Forward looking information contained herein may include, but is not limited to, statements relating to the Company’s focus on developing anti-inflammatory and anti-fibrotic therapies for the treatment of heart diseases, the molecular targets and mechanism of action of our product candidates, that cannabidiol may represent a novel strategy for treating pericarditis and preventing its complications and recurrence, the Company’s intended clinical study and trial activities and timelines associated with such activities, and the Company’s plan to advance the development of a novel subcutaneous formulation of CardiolRx™ for use in heart failure. Forward-looking information contained herein reflects the current expectations or beliefs of Cardiol based on information currently available to it and is based on certain assumptions and is also subject to a variety of known and unknown risks and uncertainties and other factors that could cause the actual events or results to differ materially from any future results, performance or achievements expressed or implied by the forward-looking information, and are not (and should not be considered to be) guarantees of future performance. These risks and uncertainties and other factors include the risks and uncertainties referred to in the Company’s Annual Information Form dated March 23, 2022, as well as the risks and uncertainties associated with product commercialization and clinical studies. These assumptions, risks, uncertainties, and other factors should be considered carefully, and investors should not place undue reliance on the forward-looking information, and such information may not be appropriate for other purposes. Any forward-looking information speaks only as of the date of this press release and, except as may be required by applicable securities laws, Cardiol disclaims any intent or obligation to update or revise such forward-looking information, whether as a result of new information, future events, or results, or otherwise.

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