GBC AG
Investment Research

Initial Coverage Report

Cardiol Therapeutics

CARDIOL™ THERAPEUTICS

One Product in two formulations, heart disease treatments in the making

Target Price: 15,77 CAD

Rating: BUY

IMPORTANT NOTE:
Please take note of the disclaimer/risk warning, as well as the disclosure of potential conflicts of interest as required by section § 85 WpHG und Art. 20 MAR

Note on research as a "minor non-monetary benefit" according to the MiFID II regulation: This research meets the requirements for being classified as a "minor non-monetary benefit". For more information, see the disclosure under "I. Research under MiFID II"

Date and time of completion of this research: 23.06.2021 (01.30 pm)
Date and time of first distribution: 23.06.2021 (03.00 pm)
Target price valid until: 31.12.2021

CARDIOL THERAPEUTICS INC.*5a,5b,6a,6b,7,11

Rating: BUY
Target Price: 15,77 CAD

Current price: 3,07 CAD
22/06/2021 / TSX / 22:00
Currency: CAD

Key Data:

ISIN: CA14161Y2006
WKN: A2PA9E
TSX: CRDL
OTCQX: CRTPF
NASDAQ: ongoing application
FSE: CT9
Number of shares[3]: 53.1M
Marketcap[3]: 180,84 m
[3] in m / in m CAD / fully diluted
Free float: 78%

Primary listing: Canada TSX
Secondary listing: Frankfurt

Accounting Standard:
IFRS

FY End: 31/12/

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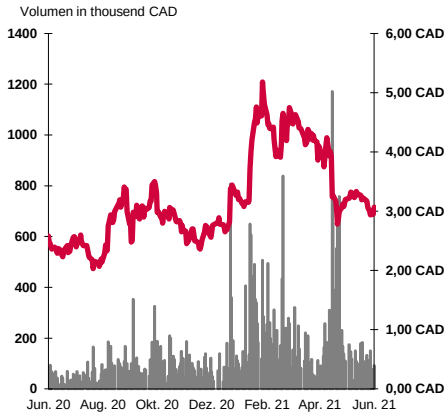
Company Profile

Sector: Biotechnology

Focus: Cannabidiol therapies for inflammatory heart disease

Management: David Elsley (President & CEO, Director), Andrew Hamer (CMO), Chris Waddick (CFO), Thomas Moffatt (CCO), Bernard Lim (COO)

Founded:2017
Headquarters: Oakville, Canada



Cardiol Therapeutics is a clinical-stage biotechnology company focused on developing innovative anti-inflammatory therapies for the treatment of cardiovascular disease.

The company portfolio is composed of three therapies in development supported by CardiolRx™ and Cortalex™, commercialized in late 2020, which is now available across Canada exclusively at Medical Cannabis by Shoppers online portal, part of the largest retail pharmacy chain in Canada.

The company has currently one FDA Phase II/III clinical program in progress to investigate cardioprotective properties of Cannabidiol for COVID-19 patients with prior history of cardiovascular disease (CVD). The company projects to apply soon (planned Q3 2021) for IND Filing for the Phase II trial for their Acute Myocarditis Clinical Development Program. The company is also developing a subcutaneous Cannabidiol formulation for Diastolic Heart Failure.

Cardiol has recently filed an uplisting application on the NASDAQ Capital Market and has completed a 22M$ CAD financing.

P&L in CAD m FY	31/12/2018	31/12/2019	31/12/2020	31/12/2021e
Sales	0	0	0	0
EBIT	-15,33	-13,78	-20,68	-18,73

Key figures in CAD m				
EV/EBITDA	-5,54	-8,18	-3,78	-4,69

**** Last research by GBC:**
Date: publication/target price in CAD/rating

** The research studies indicated above may be viewed at www.gbc-ag.de, or requested at GBC AG, Halderstr. 27, D86150 Augsburg

Financial calendar

EXECUTIVE SUMMARY

- Cardiol Therapeutics provides leadership in therapeutic trials using Cannabidiol to take advantage of major opportunities in inflammatory heart disease.
- The company has an exclusive manufacturing agreement for a Cannabidiol pharmaceutical formulation which is highly concentrated and THC free (<10 ppm).
- There is a considerable quantity of scientific evidence showing that using Cannabidiol can be beneficial as an anti-inflammatory agent.
- The management has a proven track record of strong leadership coupled with substantial industry knowledge and competence in commercializing proprietary medications.
- The team enrolled their first patients in LANCER, a Phase II/III Outcomes Trial in High-risk Patients Hospitalized with COVID-19 in April 2021.
- The phase I Single and Multiple Ascending Dose Clinical Trial showed successful Topline results for CardiolRx™ in April 2021.
- The company applied for uplisting on the NASDAQ in March 2021.
- Cardiol Therapeutics has one product on the market in Canada, Cortalex™ CBD, exclusively available online at Medical Cannabis by Shoppers Inc.
- The company raised over 50M CAD during the past 12 months, with 42.9M shares outstanding allowing for maximum future value creation for shareholders.
- Our estimates project considerable cumulative earnings of 2.982M CAD for the next 10 years with an 85% average margin.
- They have a unique opportunity to leverage the well documented and discussed benefits of Cannabidiol for three different cardiovascular disease markets, each in dire need of effective treatment.
- We believe the company to be an early takeover target in case of positive results of their COVID-19 Phase II/III trials.
- Price target: 15,77 CAD, Rating: BUY

CONTENTS

COMPANY

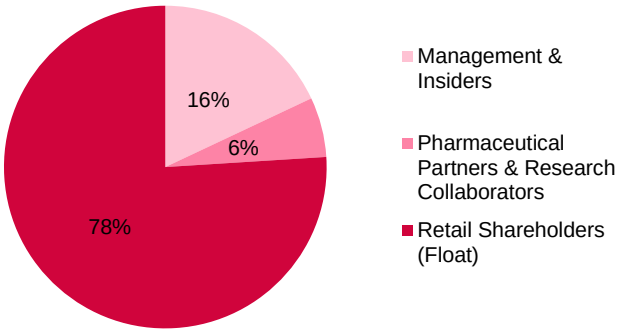
1. Factsheet

1.1. Corporate structure

Cardiol Therapeutics is a biotechnology company with offices in Oakville, Ontario. 22 employees working on and off site. They also conduct research and development all over the world through partnerships with universities and private companies. The company was incorporated on January 19, 2017. It went public on December 20th, 2018. There are no subsidiaries.

Shareholder structure	In %
Management & Insiders	16%
Pharmaceutical Partners	6%
Other Shareholders (Float)	78%
Total	100%

Sources: Cardiol Therapeutics Inc., GBC AG

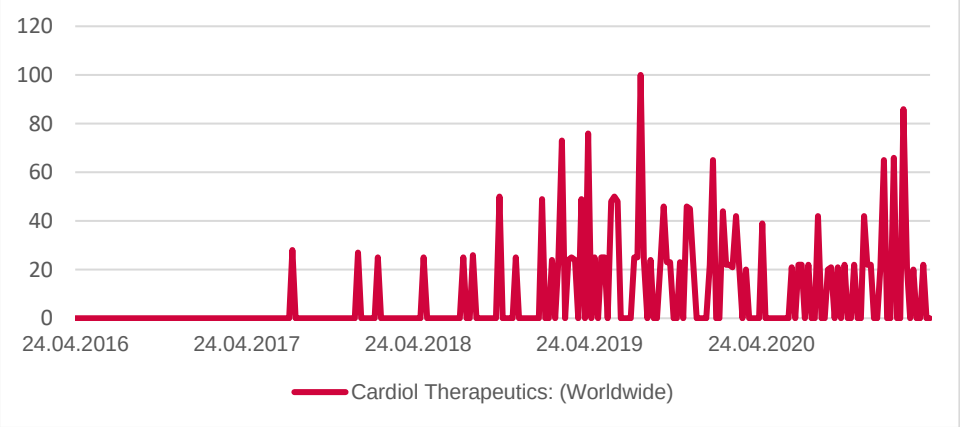


Common Shares		42.946.594
Warrants	(@ $3,25)	1.070.048
Warrants	(@ $2,50)	55.182
Warrants	(@ $4,00)	824.000
Warrants	(@ $4,60)	3.489.400
Options	(@ $2,12/5,77)	3.401.300 / weighted average $4,43)

Exchanges: WKN: A2PA9E, TSX: CRDL, OTCQX: CRTPF, FSE: CT9
NASDAQ: approval pending

1.2. Social Media footprint

Google Trends

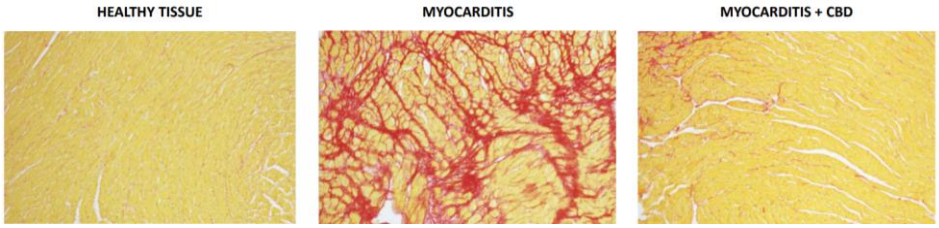


2. Business Model

2.1. Cannabidiol and the heart

In 2016, Lee W-S et al. published a research paper in *Molecular Medicine* presenting their findings on the effect of Cannabidiol on heart inflammation and fibrosis. Their results showed that "*CBD treatment markedly attenuates autoimmune myocarditis and improves myocardial dysfunction and heart failure primarily by its anti-inflammatory and antifibrotic effects."*

Section of heart tissue - Fibrosis



Source: Molecular Medicine[1]

Moreover, the authors concluded that "*these results, coupled with the proven safety of CBD in human clinical trials and its current orphan drug approval by the FDA for different neurological disorders, suggest that it has tremendous therapeutic potential in the therapy of myocarditis with different etiologies and various autoimmune disorders*".

Cardiol Therapeutics' executive team decided to not only follow this lead but to build their company on the possible benefits of the anti-inflammatory and anti-fibrotic effects of Cannabidiol. In 2017, they started developing CardiolRx, a pharmaceutical product that can be applied in the treatment of a range of heart inflammation related diseases. Currently, the company is developing three different treatments: CardiolRx COVID-19, CardiolRx Acute Myocarditis, CardiolRx Diastolic Heart failure.

CardiolRx is a pharmaceutical formulation of Cannabidiol (CBD) of high concentration (100mg/mL) and high purity (THC content is less than 10 ppm), that is manufactured under cGMP guidelines.

It has the same concentration, but higher purity, as the first FDA-approved pharmaceutical form of CBD that was developed as an orphan drug for the treatment of rare forms of pediatric epilepsy, Epidiolex®.

Why Cannabidiol?
Cardiol Therapeutics' exclusive Cannabidiol based treatment development relies on years of historical research into the specific properties of this molecule, underlining possible benefits of Cannabidiol in cardiovascular disorders and culminating in the 2016 publication mentioned above.

[1] https://molmed.biomedcentral.com/articles/10.2119/molmed.2016.00007

Selection of evidence supporting a therapeutic role for CBD in cardiovascular disorders

Disorder	Model	Conc/Dose of CBD	Summary of findings
	Preconstricted, Wistar rat aortae	10 μM, 2 h incubation	Vasorelaxation mediated by PPARγ receptor, ↑ SOD and ↓ Ca^{2+}entry
	Preconstricted human mesenteric arteries	0.1–100 μM	Acute vasorelaxation mediated by CB_1 receptor, TRPV channels, the endothelium, and nitric oxide
Diabetes	STZ-induced diabetic SD rats	10 mg kg^{-1} i.p. for up to 4 weeks	↓ in diabetes-induced hyperpermeability ↓ inflammation ↓ oxidative stress ↓ VEGF
	High glucose treated human coronary artery endothelial cells	0–6 μM, 48 h incubation	↓ ICAM-1 and VCAM-1 ↓ monocyte adhesion and trans-endothelial migration ↓ disruption of endothelial barrier ↓ superoxide production ↓ inflammation
	STZ-induced diabetic mice	20 mg kg^{-1} i.p. for 11 weeks	↓ Left ventricular dysfunction ↓ myocardial oxidative stress ↓ myocardial inflammation ↓ myocardial fibrosis ↓ myocardial nitrative stress
Myocardial infarction	LAD ligation in the SD rat	5 mg kg^{-1} i.p. (pre-ischaemia and for 7 days)	↓ infarct size ↓ infiltrating leucocytes ↓ circulating IL-6
	LAD ligation in the SD rat	50 μg kg^{-1} i.v. 10 min pre-ischaemia or 10 min pre-reperfusion	↓ infarct size ↓ ventricular ectopic beats (only when given pre-ischaemia) ↓ platelet aggregation
Stress	Conditioned fear, Wistar rats Restraint stress, Wistar rats	10 mg kg^{-1} i.p., 30 min before testing 10 or 20 mg kg^{-1} i.p., 30 min before testing	↓ HR and MAP response to stress ↓ HR and MAP response to stress Inhibited by a $5HT_{1A}$ antagonist
Stroke	Bilateral carotid occlusion, male Mongolian gerbils	5 mg kg^{-1} i.p., 5 min after surgery	Inhibited EEG flattening Inhibited hyperlocomotion ↑ survival of CA1 hippocampal neurons
	MCAO, mice	3 mg kg^{-1} i.p., immediately before and 3 h after MCAO	↓ infarct size ↑ CBF Independent of TRPV1 Inhibited by $5HT_{1A}$ antagonism ↑ CBF
	MCAO, mice	3 mg kg^{-1} i.p., immediately before and 3 h after MCAO Repeated treatment 3 mg kg^{-1} for 14 days	↑ cerebral blood flow ↑ antioxidant power Independent of CB_1 Inhibited by $5HT_{1A}$ antagonism
	MCAO, mice	3 mg kg^{-1} i.p., immediately before and 3 h after MCAO; 1, 2 or 4 h after MCAO	Inhibited neutrophil activity ↓ infarct size ↑ CBF Improved motor coordination Effective both pre- or post-ischaemia Independent of CB_1 or CB_2
Encephalitis	LPS-treated mice	3 mg kg^{-1} i.v. at the same time as LPS	↓ vasodilator effect of LPS on CBF ↓ LPS-induced BBB permeability ↓ LPS-induced expression of TNFα and COX-2

Source: British Pharmaceutical Society[2]

Concurrently, the scientific community has tried to not only identify the impacts of CBD but also to understand the mechanism and molecular pathways of CBD in the cardiovascular system.

How does Cannabidiol work?

The scientific community is still working on understanding the entire life cycle of CBD in the human body and its interaction with its different components. Confirmed properties based on available research are considerable. When looking at its anti-inflammatory properties, CBD is involved in regulating several pathways, protecting cardiomyocytes from inflammation and oxidative stress, regulating the Ca^{2+}/K^{+} intake, decreasing immune proliferation, and promoting cellular survival.

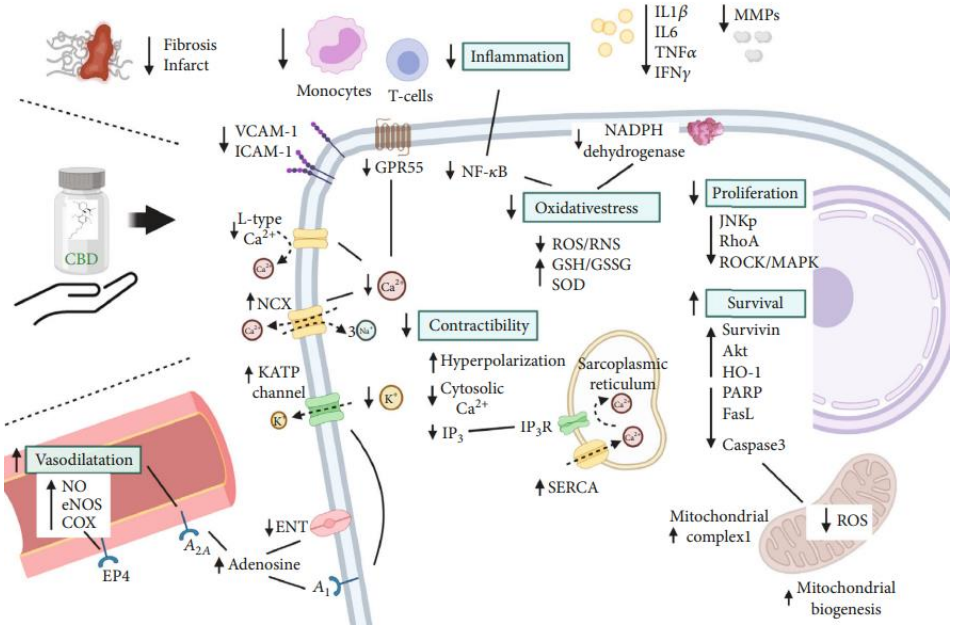
[2] https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2125.2012.04351.x

CBD also helps to protect mitochondria and regulates their biogenesis, improving the cellular energy supply. In vascular vessels, CBD causes vasodilatation, lowering blood pressure, and protecting the heart.

An exact description of how the molecules interact with the human body, resulting in these properties is yet outstanding. There are many singular proposed mechanisms, but the scientific community has not yet reached an agreement.
The authors of a study[3] published in 2020, aggregated all previous relevant research on CBD and heart disease and proposed a mechanism and molecular pathway of CBD based on current cardiovascular models. Their hypothesis is as follow:

"Based on the collected evidence in the studied models pointing to CBD as a promising cardioprotective therapy, we performed a thorough analysis of the pleiotropic mechanisms involved, as well as molecular pathways and target molecules that are, to some extent, affected by the CBD administration. We identified five main mechanisms modulated by CBD that are responsible for the beneficial effects observed in cardiac dysfunction and heart failure: (a) oxidative and nitrosative stress, (b) the inflammatory state, (c) effect on vasorelaxation, (d) the regulation of cardiac contractibility, and (e) antiproliferative and antiapoptotic properties." All these mechanisms are summarized in the following figure[4] (Arrows indicate changes in activity for each molecule/mechanism/inflammatory cell):

Mechanisms and molecular pathways of the in the cardiovascular system



Sources: J. A. Garza-Cervantes et al[5], GBC AG

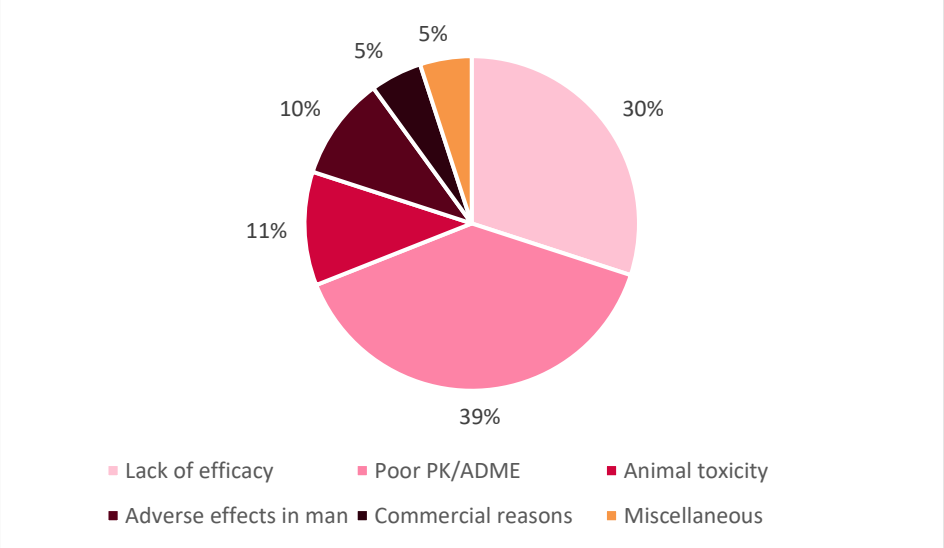
Cannabidiol Safety
Unlike other cannabinoids, CBD has an exceptional safety profile and does not pose a substantial risk to the user. The drug has even been demonstrated as safe to use for pediatric patients, another key indicator of the product's safety.

As seen in the figure below, there are several reasons why a drug would be considered unsafe and, in the following, rejected by the FDA and other public health authorities. Most

[3] http://europepmc.org/article/MED/33194003
[4] https://hindawi.com/journals/omcl/2020/4587024.pdf
[5] https://pubmed.ncbi.nlm.nih.gov/33194003/

prominent amongst these are toxicity and adverse effects, drug interaction, as well as poor PK (pharmacokinetics)/ADME (absorption, distribution, metabolism, and excretion).

Reasons for failure of drug candidate in clinical development



Source: DDW-Online, GBC AG

While a drug must be absorbed by the body to have lasting positive effects, one also wants to avoid the long-term accumulation of a foreign product in the body. Recent studies[6] have shown that oral CBD and its metabolites are found at a satisfactory level in the blood levels of patients after administration. It is, furthermore, transported quickly into tissue cells and out of the blood stream. CBD is highly lipophilic and might accumulate in adipose tissues over the long run.

To date, studies involving CBD have not shown any of the adverse effects that are associated with other cannabinoids such as THC. The molecule is generally well tolerated. Compared to cannabis, CBD also does not show any signs of abuse liability. Orally ingested CBD behaved like the placebo in all tests assessing dependency.

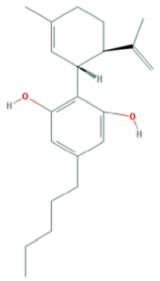
Most potential toxic effects of CBD have been explored and reviewed by scientists in the past. Cannabidiol has generally low toxicity, no effect on most nontumor cells, on psychological or biochemical parameters, and no significant effects on animal behavior.

Effects on hormonal changes and the immune system will require further research before clear statements can be made, but lower concentrations of CBD might lead to immune stimulation. Further research is also required to look at potential drug interactions of CBD with other drugs.

2.2. CBD, concentration, and purity

Cannabidiol can either come from the cannabis plant, be biosynthetically produced using for example yeast, or be pharmaceutically synthetized. Cardiol Therapeutics' management **never thought of Cannabidiol as only an extract of the cannabis plant but rather as a pharmaceutical compound**. This led them to sign, as of June 2017, an exclusive supply agreement with Dalton Pharma Services of Toronto (Dalton) to provide Cardiol Therapeutics with a proprietary pharmaceutical Cannabidiol formulation: CardiolRx.

Cannabidiol chemistry

Cannabidiol
Chemical structure  Molecular Formula: C21H30O2 Molecular Weight: 314.469 g/mol

Source: World Health Organization

Dalton is a leading North American cGMP pharmaceutical manufacturer. At the time of the agreement, Dalton was the only Health Canada approved and FDA registered company in Canada licensed to produce pharmaceutical Cannabidiol.

Dalton's unique manufacturing method allows, to our knowledge, the **highest level of purity for high concentration oral CBD formulations with virtually undetectable levels of THC (<10ppm) on the market**.

The agreement with Dalton is one of the cornerstones of Cardiol Therapeutics' business plan. It provides them with Cannabidiol that has two distinctive specifications: high concentration and great purity.

High concentration

All the company's treatments are based on CardiolRx, which contains 100 mg of Cannabidiol per ml. Using high concentration CBD may reduce stress and anxiety, has a high level of antioxidants, and increased anti-arthritic and anti-inflammatory effects which may help relieve inflammatory pain.

The latest research, reviewing over 35 trials involving Cannabidiol in different dosage concluded there was a tendency of studies with positive outcomes to have used higher doses of CBD[7].

Following analysis of over 27 trials, another study[8] showed that, on the one hand, the maximum concentration of CBD in the body can be reached relatively faster when inhaling the compound, administering the drug in a chronic fashion or in higher doses, or ensuring that the intake happens in a fed state or in a lipid formulation. On the other hand, although an increase in dose corresponds with an increase in maximum concentration (Cmax) levels, the Cmax between the higher doses of CBD does not greatly differ, suggesting a saturation effect (e.g., between 400 and 800 mg).

Pure CBD without traces of THC

In its traditional form from cannabis, CBD medication can be linked to the possibility of becoming intoxicating by residual THC. For children, young adults under 25, workers that

[7] https://doi.org/10.1111/bcp.14038
[8] https://www.frontiersin.org/articles/10.3389/fphar.2018.01365/full

cannot be intoxicated at work, or the elderly, having access to a CBD formulation that does not contain intoxicating amounts of THC is of the upmost importance. These consumers represent an important part of the medical CBD market.

One of the main issues in the medicinal cannabinoid market is purity. When clients are looking for a high concentration of CBD, they often sacrifice product purity because the levels of THC and other impurities rise significantly the more concentrated the CBD is. This issue can prove to be a real challenge for the patients mentioned above.

Dalton's proprietary CBD formulation ensures the highest purity product to our knowledge. Additionally, as there are no cannabis plants involved but only a pharmaceutical synthesis, the content from bottle to bottle is perfectly similar. This ensures that no other compounds except Cannabidiol are interacting in the human body when administrating the drug. This is critical to any future FDA approvals.

2.3. Cardiol Therapeutics product line

Cortalex – commercially available CBD formulation product

Source: Shoppers drug mart[9]

Cortalex is the company's commercial oral CBD formulation product. It is pharmaceutically produced and formulated to be consistent from batch to batch with proven purity and stability. Containing less than 10 parts per million THC, it is considered THC free. The company's exclusive manufacturing partner, Dalton Pharma Services, is cGMP compliant and meets the highest standards set by the pharmaceutical industry.

To the best of our knowledge, of the high concentration oral CBD formulations currently available in the Canadian medical market, Cortalex is by far the purest, containing virtually undetectable levels of THC (<10ppm).

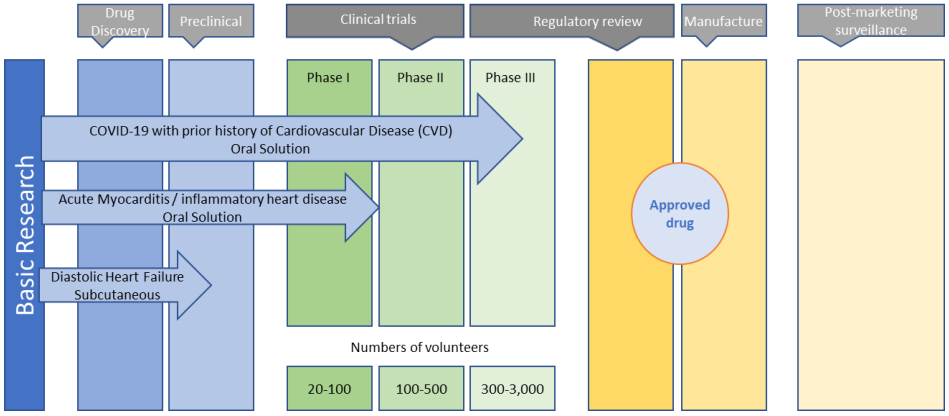
CardiolRx – the corner stone of the company's product pipeline
Cardiol Therapeutics' focus is CardiolRx, a medical product based on high concentration pharmaceutically synthetized Cannabidiol. The same product will be available to use in a variety of treatments against several diseases. Currently, the company is researching treatments for Acute Myocarditis, Diastolic Heart Failure, and even COVID-19 cases with a prior history of, or risk factors for, cardiovascular disease.

While the development of the drug as a treatment against Diastolic Heart Failure is still in the pre-clinical phase, clinical trials have started for the other two research vectors. Acute Myocarditis treatment Phase I was just completed. The clinical trial for treatment of COVID-19 for patients with a prior history of, or risk factors for, CVD is a potentially

[9] https://cannabis.shoppersdrugmart.ca/en_CA/products/Cortalex-Cardiol-Therapeutics-Cortalex-100-CBD-Oil-Hybrid/222

registrational Phase II/III trial. Phase III trials are the last step before going under regulatory review and the approval process.

Cardiol Therapeutics product pipeline



Sources: Cardiol Therapeutics, GBC AG

2.4. Historical company developments

Cardiol Therapeutics was founded in January 2017. The idea behind the company came from a paper published by Lee W-S et al. that described the positive impact of Cannabidiol on heart inflammation and fibrosis. The management saw that there was a unique occasion to develop treatments of heart failure diseases based on this research.

They then lay the pillars to a solid foundation on which the company still relies today: they signed a nanotechnology exclusive global license and an exclusive supply agreement for pharmaceutical Cannabidiol at high concentration and high purity.

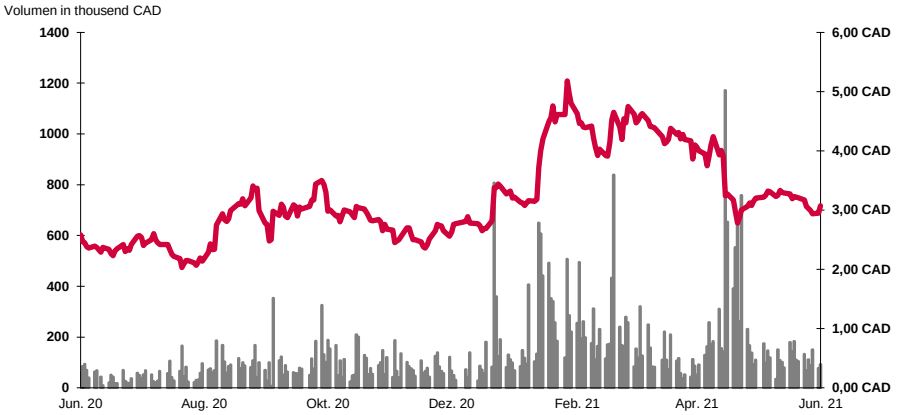
The owners took the company public at the end of 2018 and have since delivered important achievements for their treatments in development.

More specifically, the company achieved the following milestones during the past 15 months:

- ✓ Launched and marketed Cortalex, the Company's commercial Cannabidiol product, in the >$600 million Canadian cannabinoid medical market
- ✓ Initiated development of a subcutaneous formulation of CardiolRx for treatment of chronic heart failure, a leading cause of death and hospitalization in North America
- ✓ Applied for uplisting to NASDAQ with the goal of significantly increasing U.S. investor awareness

As discussed in our research note (published 03/29/2021) the company in the meantime has reached the following objectives:

- ✓ Announced data from recently completed Health Canada approved Phase I study for Acute Myocarditis treatment
- ✓ First patient enrolled in Cardiol's Phase II/III Lancer Trial of CardiolRx for COVID-19 patients with a prior history of, or risk factors for, cardiovascular disease.



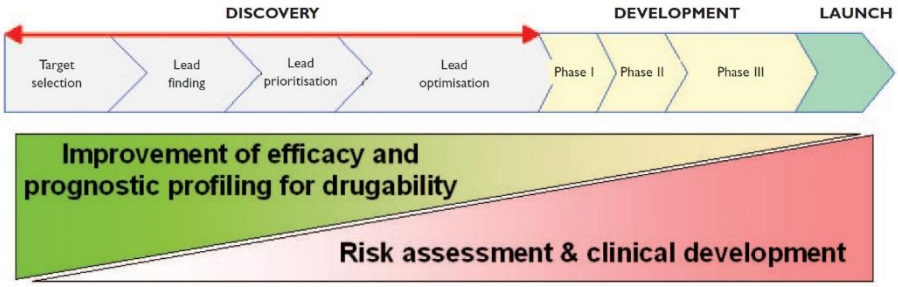
Sources: Cardiol Therapeutics Inc., GBC AG

2.5. Corporate strategy

Skipping discovery
The common pharmaceutical business model does not apply to Cardiol Therapeutics. Usually, drug development involves the following steps: drug discovery, development, and launch.

The company took a different approach by focusing on the known anti-inflammatory properties of Cannabidiol, effectively eliminating the entire discovery phase. Cardiol Therapeutics then targeted heart tissue inflammation conditions and developed therapeutic candidates that can correct or offset these heart injuries.

Common strategy for drug development



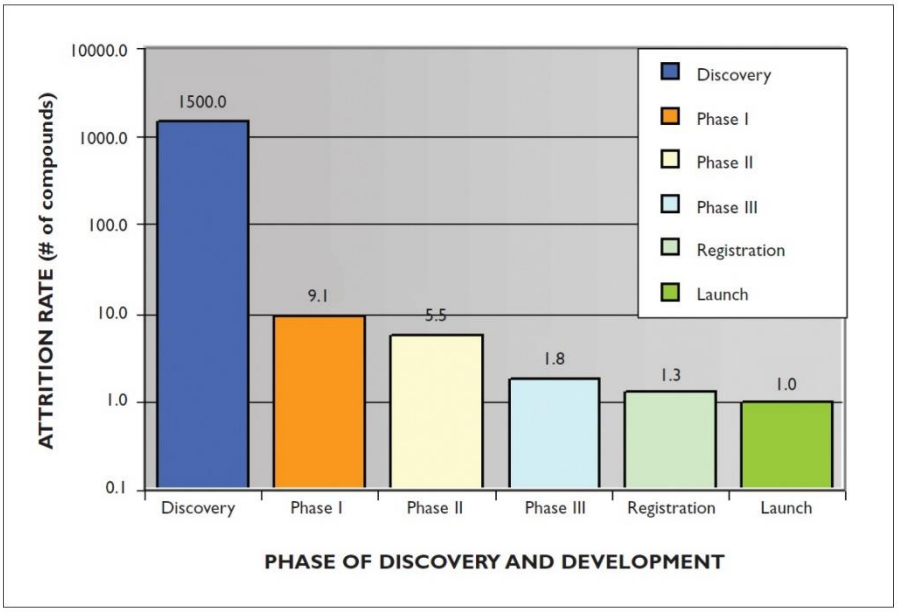
Sources: DDW, GBC AG

The benefits for investors when skipping discovery are important savings in years of R&D assessing different leads and ideas as well as an important costs reduction. This results in a lower shareholder dilution and a shorter exit strategy for both management and investors in case of a takeover. By developing treatments from a known and well-researched molecule, the company can rely on historical results and benefit from the collective efforts of the scientific community studying the pharmaceutical aspects of Cannabidiol. This significantly reduces the unknown factors faced by a company developing a new drug on its own in accordance with the traditional business model. This strategy favorably rises the potential positive outcomes of current and future trials.

De-risking Treatment Development
When comparing the following graph with the current development stage of Cardiol Therapeutics' Cannabidiol-based treatments, it clearly shows that the fact of having skipped the drug discovery phase allowed the company to greatly de-risk their ventures. The attrition rate (and consequently, risks) is highest during the discovery phase and greatly reduces when moving along the trial phases. Given that the treatment for Acute Myocarditis

has passed the Phase I stage of clinical trials and the treatment for COVID-19 patients with a prior history of cardiovascular disease has reached the Phase II/III stage, one can safely assume that the attrition rate, costs, and risks faced by Cardiol Therapeutics are in constant decline.

Attrition rate of drug candidates



Sources: DDW, GBC AG

Peer review

We have identified two companies with whom Cardiol Therapeutics treatments and business strategy can be compared: GW Pharmaceutical and MyoKardia Inc.

Both companies were acquired during the past 8 months, following an FDA approval for GW Therapeutics and a conclusive Phase III trial for MyoKardia Inc.

Recent M&A activity

	MyoKardia Inc.	GW Pharmaceuticals PLC
Acquired by	Bristol Myers Squibb	Jazz Pharmaceuticals
Acquisition date	October 2020	February 2021
Acquisition price	$13.1 billion (all cash)	$7.2 billion (93% cash)
Completion date	November 2020	May 2021
Leading treatment	**Mavacamten**	**Epidiolex (Cannabidiol)**
Target	Treatment of Obstructive Hypertrophic Cardiomyopathy (“HCM”)	Treatment of seizures associated with Lennox-Gastaut Syndrome (LGS), Dravet Syndrome and Tuberous Sclerosis Complex (TSC)
USA Market Patient	66,000 diagnosed	32,000
Phase when acquired	Phase III completed	FDA approved
Pipeline leading product	Danicamtiv	Nabiximols
Phase when acquired	Phase IIa completed	Phase III ongoing
Target	Genetic DCM and atrial fibrillation in HFrEF	Treatment of spasticity associated with Multiple Sclerosis and spinal cord injury

When comparing the current situation of Cardiol Therapeutics and the transaction metrics for GW Pharmaceutics and MyoKardia, we can appreciate the possible increase in market cap that awaits the company in case of a successful CardiolRx COVID-19 Phase II/III trial. This trial is a proof of concept for their treatments currently in development. If their trial is successful, Cardiol Therapeutics would become a target for acquisition.

Importance of acquisition in major pharma revenues

	Pfizer	J&J
Total products	44	18
Third party product	34	16
% Of all revenues generated by acquisition products	86%	89%

Research shows that major pharma companies such as Pfizer or J&J rely almost exclusively on R&D firms to develop new treatments. In a sense, one could say that even big pharma companies prefer to skip the drug discovery phase and rather acquire a product with proof of concept. The existence of Pfizer and J&J as profitable pharmaceutical manufacturers is dependent on the acquisition of drugs invented by third parties.[10].

Continuous R&D

Another advantage that Cardiol Therapeutics has integrated into their corporate strategy are the company's exclusive partnerships which allow them to concentrate their effort on the development of new possible treatments rather than costly R&D and maintaining their advantageous position of skipping discovery.

Exclusive Partnerships

Objective	Company	Current Status
Development of high concentration high purity Cannabidiol	Dalton	Completed
Nanoformulations of anti-inflammatory drugs	University of Alberta	Ongoing
CBD nanoformulations	University of Alberta	Ongoing
Research and development of proprietary therapeutics for the treatment of heart failure	TecSalud del Tecnologic de Monterrey & Nano4Heart (3M CAD research program)	Ongoing
Investigate the therapeutic potential of Cannabidiol formulations that target inflammation in a model of hypertension-induced heart failure	TecSalud del Tecnologic de Monterrey & Nano4Heart	The research is expected to be completed in 2021
Investigate functionality of the Corporation's in-licensed patented nanotherapeutics	Houston Methodist DeBakey Heart & Vascular Center	Completed
Build upon the initial research in an experimental model of heart failure	Houston Methodist DeBakey Heart & Vascular Center	The research is expected to be completed in 2021
Investigating ageing and its effects on inflammation, particularly neuroinflammation	School of Medicine at Trinity College	The research is expected to be completed in 2022

[10] Analysis: Large pharma companies do little new drug innovation - STAT (statnews.com)

Patent Portfolio
The company is building an extensive patent portfolio as seen in the table underneath:

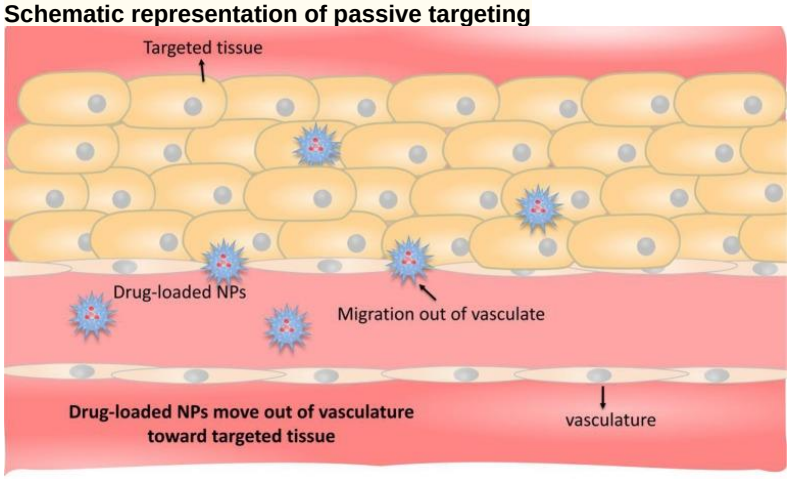
	Description
Patent Family 1	Poly (Ethylene Oxide)-Block-Poly (Ester) Block Copolymers (the "Block Copolymer Family")
Patent Family 2	Amphiphilic Block Copolymers, Micelles, And Methods for Treating and/or Preventing Heart Failure
Patent Family 3	Stable Medicinal Cannabidiol Compositions
Patent Family 4	Stable Oral Cannabidiol Composition
Patent Family 5	Parenteral Cannabidiol Compositions for Treating Heart Conditions
Patent Family 6	Injectable Cannabinoid Formulations
Patent Family 7	Cannabidiol For Use In Improving Outcomes In Subjects With Covid-19

It is important to underline that Cardiol Therapeutics currently has a sole, exclusive, worldwide, irrevocable, royalty bearing license to exploit the Block Copolymer Family for the following fields of use:

- the delivery of any Cannabinoids for any and all human or animal disease indications and any derivatives thereof.

- the delivery of any drugs or classes of drugs currently used or developed in the future to diagnose or treat cardiovascular and/or cardiopulmonary disease, heart failure and/or cardiac arrhythmias in humans and animals, including Sildenafil, Pirfenidone, Rapamycin, Methotrexate, Amiodarone, Cannabinoids, blockers of HSP60 activity or inhibitors of production and/or transport of HSP60 and any derivatives of any of them.

Schematic representation of passive targeting



Source: National library of Medicine [11]

Due to the size and surface characteristics of a portion of nanomaterials, they are rapidly cleared in the blood during intravenous injection, making nanomaterials unsuitable for drugs that require long cycle times. In this case, nano-coating technology can be applied to the nano-system for certain concealment, and the rate of administration of the coating agent can be also controlled and adjusted.

[11] https://pubmed.ncbi.nlm.nih.gov/32083068/

Nano Drug Delivery Systems (NDDS) are seen as an important part of the future of drug delivery for CVD as they could target more efficiently the targeted tissue while exhibiting biocompatibility, non-toxicity, and no teratogenicity. Its degradation products, including oligomerization and final products, have no toxic effect on cells, and can coexist stably with most drugs[12].

2.6. Key Management and Directors

David Elsley, MBA – President and Chief Executive Officer
Mr. Elsley has an MBA from the Richard Ivey School of Business, University of Western Ontario, and extensive experience in developing, financing, and running high-growth biotech corporations. He founded Vasogen Inc. in 1990, a biotech company specializing in developing therapies for treating heart failure and other inflammatory conditions. Mr. Elsley led Vasogen's growth from a startup to a 250+ employee company with offices in Canada, the US, and Europe. During his leadership, Vasogen Inc. completed international multicenter pivotal Phase III clinical trials for two anti-inflammatory therapies. Vasogen listed on the TSX and the Nasdaq, raised $200 million and was worth more than $1 billion. In 2017 he co-founded Cardiol Therapeutics of which he is now president and CEO.

Andrew Hamer, MB, ChB – Chief Medical Officer
Dr. Andrew Hamer holds a Bachelor of Medicine and Surgery from the University of Otago in New Zealand. After clinical research training in New Zealand and London, UK, he trained in cardiology at Deaconess Hospital at Harvard Medical School, in Boston. Dr. Hamer practiced cardiology and internal medicine for 19 years and most notably worked as Chief Cardiologist at Nelson Hospital, while also serving as Chairman of the New Zealand Cardiac Network.
Starting in 2013 Dr. Hamer spent two years as VP Medical Affairs for Capricor Therapeutics Inc., where he was involved in the development of novel therapeutics for heart disease and the supervision of clinical operations.
From 2015 to March 2021, he was Global Development Medical Director, Cardiometabolic and Global Development Executive Director, Cardiometabolic at Amgen Inc., where he oversaw the development of the US $900 million-revenue earning drug Repatha. He designed and executed several multi-center clinical trials in support of FDA and international regulatory filings.
Dr. Hamer has, moreover, been involved in several prominent clinical trials over the years, many of which were for treatments for acute coronary syndrome, heart failure, hypertension, cholesterol disorders, atrial fibrillation, and diabetes. Since March 2021 he is Chief Medical Officer at Cardiol Therapeutics.

Eldon R. Smith, OC, LLD (Hon), MD, FCAHS, FCCS, FRCPC – Chairman
Dr. Eldon R. Smith graduated with honors from Dalhousie University. After his training in Canada, the UK, and the US, he joined the faculty at Dalhousie in 1973. From 1980, he has been Head of Cardiology, Chairman of Medicine, Associate Dean for Clinical Affairs and Dean of Medicine at the University of Calgary.
Dr. Smith has received many awards including the Medal of Service from the Canadian Medical Association and in 2005, Dr. Smith became an Officer of the Order of Canada. He has published over 250 papers and has worked in numerous institutions; he was President of the Canadian Cardiovascular Society (CCS) and the Association of Canadian Medical Colleges. He has been a member on several public boards and a director of more than ten different public companies over the past two decades. He's been Chairman at two companies and a Lead Director for two others.
He established and currently leads the Peter Lougheed Medical Research Foundation. He was named chair of the Steering Committee for the Canadian Heart Health Strategy in

[12] doi:10.3389/fbioe.2019.00489

2006. At present, he is a Director of Zenith Capital Corp and Chairman of the Board at Cardiol Therapeutics.

Guillermo Torre-Amione, MD, PhD – Director
Dr. Guillermo Torre-Amione is former chief of the Heart Failure Division and a former medical director of Cardiac Transplantation at the Houston Methodist DeBakey Heart & Vascular Center. He also is a senior member at The Methodist Hospital Research Institute, professor of medicine at the New York Cornell University, and President of TecSalud, an academic medical center and medical school of the Instituto Tecnologico y de Estudios Superiores de Monterrey (ITESM) in Mexico.
In the Gene and Judy Campbell Laboratory for Cardiac Transplant Research, Dr. Torre-Amione focuses on research about heart failure, heart transplant, and the immune response's impact on heart failure progression. He led a series of clinical studies, which resulted in a Phase II clinical trial for a new method of neurostimulation in heart failure.
Dr. Torre-Amione has published more than 170 manuscripts in peer-reviewed journals.

Deborah Brown, MBA – Director
Ms. Deborah Brown has an MBA from University of Western Ontario's Ivey School of Business, a B.Sc. (Hons). from the University of Guelph and completed the Merck Executive MBA Program at the University of Hong Kong, INSEAD. She is Managing Partner at Accelera Canada Ltd., a consultancy firm providing market strategies for biopharmaceutical companies in Canada. She was Executive Vice President of Neuroimmunology for the U.S. divisions and President and General Manager of the Canadian divisions of EMD Serono (a division of Merck KGaA, Merck Serono). Ms. Brown led EMD Serono Canada through a period of unprecedented growth from a small $10 million association to a mid-sized pharma business with a portfolio of $150 million in revenues.
Ms. Brown served on the Board of Directors of the National Pharmaceutical Organization (now Innovative Medicines Canada) from 2007 to 2014 and chaired it in 2012. She is currently part of the Boards of Oncolytics Biotech Inc., Sernova Corp., the Strategic Executive Advisory Council for Canadian Cancer Trials Group, and her local SPCA.

Peter Pekos, BSc, MSc – Director
Mr. Pekos has a Chemistry/Biochemistry Double Specialist Degree with a Minor in Biology from the University of Toronto and a master's degree in synthetic chemistry from York University.
Mr. Pekos founded Dalton Pharma Services in 1986 in an incubator at York University creating specialty chemical compounds. Dalton offers pharmaceutical and biotech clients a diverse range of integrated services. This includes research on specialty ingredients, analytical support, medicinal chemistry, formulation, cGMP manufacture of solid dosage forms, and cGMP aseptic fill in vials and syringes. The company also provides custom peptides and conjugation of active pharmaceutical ingredients and fluorophores with polymers and antibodies. Dalton's clients today include the world's largest pharmaceutical companies.
In 1992, Mr. Pekos founded Ashbury Biologicals, Inc., a phyto-pharmaceutical company, and since then several other companies that focused on advanced materials and pharmaceutical development tools.

Mr. Pekos has served on the boards of Lab Business and Critical Outcome Technologies, Inc. Since 2011 he is founding chairman of ventureLAB, a regional innovation center providing services to the biotechnology innovation ecosystem in southern Ontario.

Colin G. Stott, BSc (Hons) – Director

Mr. Stott graduated from Loughborough University of Technology, U.K. as well as the Welsh School of Pharmacy, Cardiff University, U.K. He has published over 20 research papers and is a named inventor on 17 international patent applications. He also has clinical R&D experience in a great variety of fields: cardiology, oncology, urology, dermatology, metabolic disorders, neurology, hematology, and organ transplantation.

Mr. Stott has nearly 30 years of experience working in pre-clinical and clinical development, with specific expertise in the development of cannabinoid-based medicines.

From 2001 to 2019 he was R&D Operations Director and Scientific Affairs Director, International, at GW Pharmaceuticals plc, a company which focuses on cannabinoid-based treatments. There he participated in the Marketing Authorization Application submission and approval of Sativex and the New Drug Application submission of Epidiolex, an orphan drug for the treatment of rare forms of paediatric epilepsy. More recently, he was part of the Medical Affairs team responsible for the international launch of Epidiolex.

From 2019 to 2020 he was Chief Operating Officer at Alinova Biosciences Ltd and founded Phytotherapeutix Ltd in December 2020.

PRODUCT PIPELINE

1. Cardiol Covid-19 treatment

1.1. COVID-19: How does it affect the body?

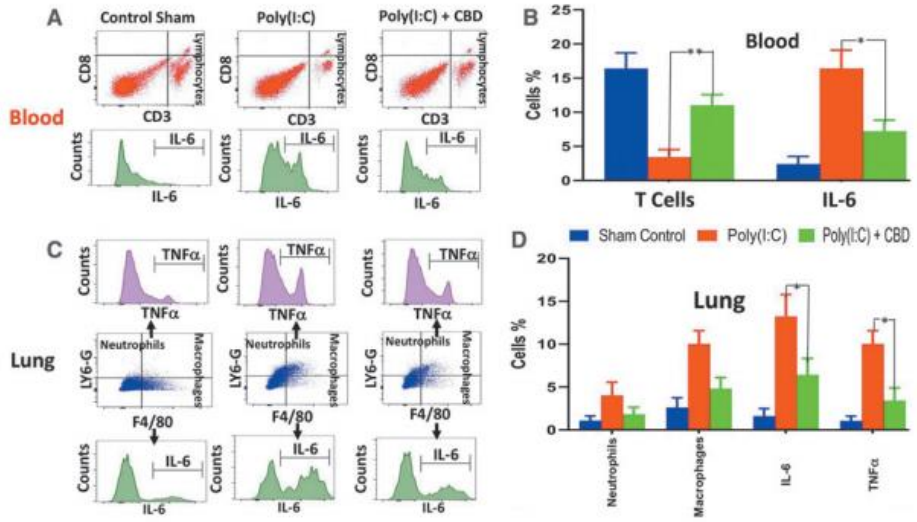
The current pandemic is caused by a coronavirus, SARS-CoV-2, that acts in the human body in two distinct immune response stages. The first phase triggers a mild response from COVID-19 positive patients and can evolve to the second phase which provokes a virally induced cytokine storm syndrome. This is the acute phase of the disease. Research has identified elevated levels of many cytokines, more specifically interleukin (IL)-6 and IL-8, tumor necrosis factor alpha (TNFα) and C–C Motif Chemokine Ligand 2 (CCL2).

1.2. Current research on Cannabidiol and the Corona virus

Among all cannabinoids, Cannabidiol (CBD) has demonstrated potent anti-inflammatory effects in a variety of pathological conditions. Therefore, it is logical to explore whether CBD can reduce the cytokine storm and treat acute respiratory distress syndrome (ARDS).[13]

Hesam Khodadadi et all, in their publication, dated November 2020, *Cannabidiol Modulates Cytokine Storm in Acute Respiratory Distress Syndrome Induced by Simulated Viral Infection Using Synthetic RNA*[14] showed that the administration of CBD resulted in lower level of the proinflammatory cytokines, lower level of IL-6 and higher level of T-Cells. This proposes that the cytokine storm in COVID-19 patients could be regulated.

Anti-inflammatory effect of CBD after intranasal Poly(I:C) treatment.

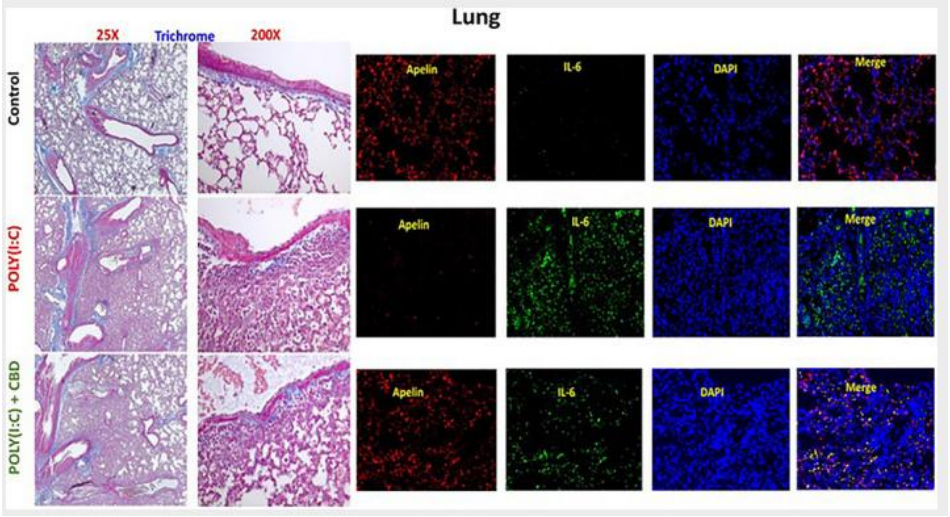


Source: Cannabis and Cannabinoid Research[15]

In their following research, the team discussed the possibility that CBD may ameliorate the symptoms of ARDS through up-regulation of apelin, a peptide with significant role in the central and peripheral regulation of immunity, CNS, metabolic and cardiovascular system[16].

[13] J Cell Mol Med . 2020 Nov;24(21):12869-12872. doi: 10.1111/jcmm.15883. Epub 2020 Oct 15.
[14] Khodadadi H, Salles E´L, Jarrahi A, Chibane F, Costigliola V, Yu JC, Vaibhav K, Hess DC, Dhandapani KM, Baban B (2020) Cannabidiol modulates cytokine storm in acute respiratory distress syndrome induced by simulated viral infection using synthetic RNA, Cannabis and Cannabinoid Research 5:3, 197–201, DOI: 10.1089/can.2020.0043
[15] https://www.liebertpub.com/doi/10.1089/can.2020.0043
[16] (DOI): 10.1111/jcmm.15883

CBD improved the symptoms of Poly(I:C) ‐ induced ARDS and normalized the apelin expression in the lung tissues



Source: J Cell Mol Med.[17]

1.3. COVID-19 FDA Approved treatments: an overview.

The FDA has two different types of approvals. They can issue an emergency use authorization or an FDA approval. These two are not equivalent and have different purposes and uses.

(Regular) FDA Approval process
The FDA determines if the clinical data and other information show that the drug is safe and effective for its intended use and if the product can be made according to federal quality standards. The FDA has determined, based on substantial evidence, that the drug is effective for its intended use, and that the benefits of the drug outweigh its risks when used according to the product's approved labeling. This is a full FDA approval that allows commercialization of the drug in the USA and serves as a pillar for drug commercializing in Canada and Europe.

Emergency Use Approval (EUA)
In certain emergencies, the FDA can issue an EUA to provide access to medical products that may potentially be used when there are no adequate, approved, and available options. The FDA makes a product available to the public based on the best available evidence, without waiting for all the evidence that would be needed for full FDA approval. When evaluating an EUA, the FDA carefully balances the potential risks and benefits of the products based on the data currently available. EUAs are effective until the emergency declaration ends. EUAs can also be revised or revoked by the FDA at any time as they continuously evaluate the available data and patient needs during the public health emergency.

[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7686987/

Current authorized treatments of COVID-19 positive patients.

Treatment	COVID-19 positive patients	COVID-19 treatment authorization	COVID-19 Proven effective[18]
Casirivimab and Imdevimab (monoclonal antibodies)	Severe symptoms, not hospitalized	Emergency use authorization (EUA). Treatment non-FDA approved	No.
Bamlanivimab and Etesevimab (monoclonal antibodies)	Severe symptoms, not hospitalized	Emergency use authorization (EUA). Treatment non-FDA approved	No. Negative expectation against South African and Brazil variants[19]
Dexamethasone (corticosteroids)	Severe symptoms and hospitalized	NIH COVID-19 treatment guidelines recommend the use of dexamethasone in certain people hospitalized with severe COVID-19.	No. No proven benefit in patients who did not need respiratory support. Important side effects.
Remdesivir	Severe symptoms and hospitalized	Emergency use authorization (EUA). Treatment non-FDA approved[20]	No. Clinical trials suggest that in these patients, Remdesivir may modestly speed up recovery time.
Baricitinib in combination with Remdesivir	Severe symptoms and hospitalized	Emergency use authorization (EUA). Treatment non-FDA approved	There is not yet enough evidence to support the use of this therapy instead of Dexamethasone with or without Remdesivir.
Anticoagulation drugs ("blood thinners") low-dose heparin or enoxaparin	Severe symptoms and hospitalized	FDA approved against blood cloth.	Help prevent blood clots
Convalescent plasma	Severe symptoms and hospitalized	Emergency use authorization (EUA). Treatment non-FDA approved	No[21] Compared to placebo and standard treatment, convalescent plasma did not significantly improve risk of death, length of hospital stays, or the need for a ventilator.
Hydroxychloroquine	All positive patients	NIH treatment guidelines recommend against the use of Hydroxychloroquine for COVID-19, in both hospitalized and non-hospitalized patients.	Researchers reported that Hydroxychloroquine did not result in any clinical benefits for adults hospitalized with respiratory illness from COVID-19, compared with a placebo.

Source: Harvard Medical School[22]

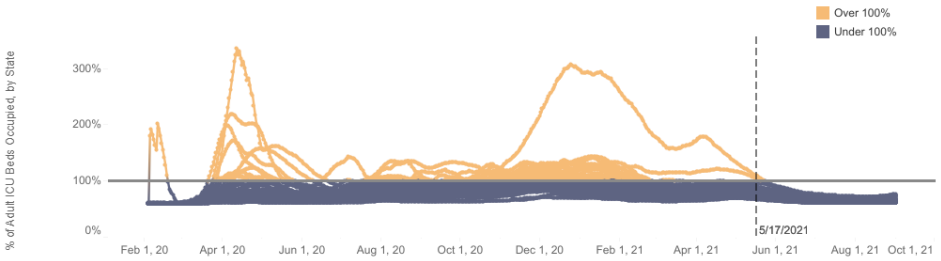
[18] https://www.health.harvard.edu/diseases-and-conditions/treatments-for-covid-19 (consulted 08.05.2021)
[19] Fact Sheet For Health Care Providers Emergency Use Authorization (Eua) Of Bamlanivimab And Etesevimab (fda.gov) (consulted 08.05.2021)
[20] FDA's approval of Veklury (remdesivir) for the treatment of COVID-19—The Science of Safety and Effectiveness
[21] Convalescent Plasma to Treat COVID-19: Possibilities and Challenges | Infectious Diseases | JAMA | JAMA Network
[22] https://www.health.harvard.edu/diseases-and-conditions/treatments-for-covid-19

As seen in the table above, there is no FDA approved treatment for COVID-19 positive patients, only EUAs. Additionally, at best, treatments with EUA drugs have limited, if any, effectiveness against the disease symptoms and can result in important side effects as seen for the drug Dexamethasone.

1.4. COVID-19 and heart disease

Even as the current crisis slows down in some parts of the world, COVID-19 continues to rampage other parts of the world. A treatment of acute symptoms that relieves intensive care unit (ICU) beds is one of the most critical answer to this pandemic.

% of adult ICU beds occupied by states



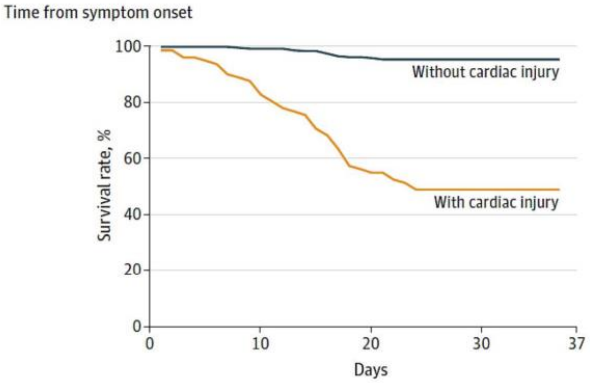
Sources: American hospital association[23], GBC AG

The latest research[24], analyzing over 900,000 COVID-19 hospitalizations that occurred through November 2020, has shown that heart failure precondition is the 4th cause, after diabetes mellitus, total obesity, and hypertension, with 12%, of the total attributable hospitalization in the U.S due to COVID-19. These statistics vary according to different metrics, particularly age. Older adults with diabetes, heart failure, or hypertension were more likely to be hospitalized than younger people with the same conditions.

The leading cause of COVID-19 mortality is respiratory failure due to acute respiratory distress syndrome[25]. It was noted that COVID-19 positive patients with preexisting heart conditions had a higher mortality rate than those without cardiac injury[26]. Patients with cardiac injury were, moreover, more likely to require mechanical ventilation and complications were more common with these patients while hospitalized.

[23] https://metricvu.aha.org/dashboard/covid-bed-shortage-detection-tool
[24] https://doi.org/10.1161/JAHA.120.019259
[25] Mehta, P. et al. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 395, 1033 (2020).
[26] Shaobo Shi et al., 'Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China', JAMA Cardiology, 25 March 2020

Mortality rate for patients with and without previous cardiac injury



Source: National Library of Medecine[27]

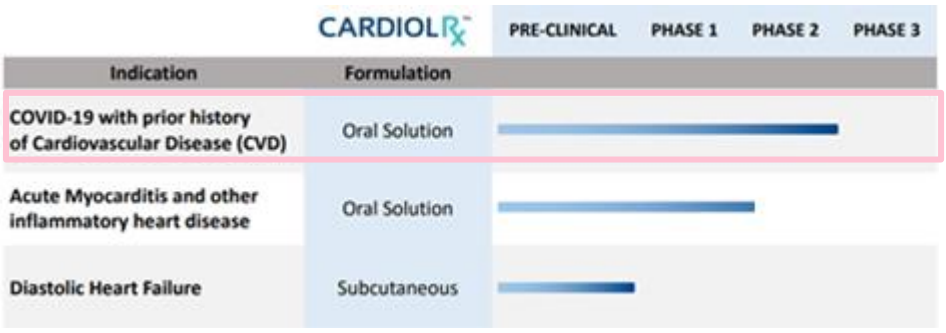
Another recent research[28] studied 100 German patients recently recovered from a COVID-19 infection. Cardiac blood markers and cardiovascular magnetic resonance (CRM) revealed cardiac involvement in 78 patients (78%) and ongoing myocardial inflammation in 60 patients (60%), independent of preexisting conditions, severity and overall course of the acute illness, and time from the original diagnosis.

> *"These findings may provide an indication of potentially considerable burden of inflammatory disease in large and growing parts of the population […]. Although the long-term health effects of these findings cannot yet be determined, several of the abnormalities described have been previously related to worse outcome in inflammatory cardiomyopathies."*

Even though the COVID-19 crisis could potentially dissipate soon given the lower number of positive cases, the heart inflammatory injuries withstood by the patients, (both with acute symptoms that required hospitalization and with mild symptoms that required no hospitalization) could persist for a long time and need special care in order to treat or resorb such injuries.

In conclusion, this lets us believe that the current state of the pandemic still demands three solutions: preventive treatment to reduce hospitalization of COVID-19 positive patients (phase 1 of the disease), treatment of the acute phase of the infection (and death rate), as well as treatment to reduce the long-term consequences on heart tissue inflammation caused by COVID-19 even on non-hospitalized patients.

1.5. Cardiol Therapeutics proposed treatment: COVID-19 CardiolRx



Sources: Cardiol Therapeutics, GBC AG

[27] https://pubmed.ncbi.nlm.nih.gov/32211816/
[28] JAMA Cardiol. 2020;5(11):1265-1273. doi:10.1001/jamacardio.2020.3557

In September 2020, Cardiol Therapeutics received the FDA Investigational New Drug (IND) approval which allowed them to debut a Phase II/III study, called the Lancer Trial, to evaluate the efficacy and safety of CardiolRx™ in a double-blind, placebo-controlled trial for 422 hospitalized COVID-19 patients with a prior history of, or risk factors for cardiovascular disease (CVD).

In December 2020, the company appointed a contract research organization (CRO), Worldwide Clinical Trials, to conduct the trial on their behalf. This company has extensive experience in both COVID-19 and cardiovascular disease trials. They employ over 1,900 professionals in North and South America, Europe and Asia and have a footprint in more than 60 countries.

The study is designed to assess the efficacy, safety, and tolerability of CardiolRx in preventing cardiovascular complications in hospitalized patients, with a confirmed diagnosis of COVID-19 within the previous 48 hours, and who have pre-existing CVD and/or significant risk factors for CVD. The trial is currently planned to be conducted in major centers in the United States, where the prevalence of COVID-19 remains high. However, if the enrollment is not going as planned, the company could also resort to other major centers in other countries, where the COVID-19 situation could allow for more patients qualified for this treatment.

Patients will be receiving the following treatment for 28 days: CardiolRx 2.5 to 7.5 mg/kg of body weight taken twice daily orally with food. The comparator will be a placebo that will follow the same dosage. (1:1 ratio of patients receiving CardiolRx and placebo)

To make these assessments, the trials will be examining the following primary outcomes of the cardioprotective effects of CardiolRx versus placebo.

Primary Outcome measures	Metric	Time frame
All-cause mortality	Proportions of patients not surviving	28 days post randomization
Requirement for ICU admission and/or ventilatory support	Proportions of patients needing ICU admission and/or ventilatory support	28 days post randomization
CV complications	HF, AMI, myocarditis, new sustained arrhythmia, or stroke	28 days post randomization

Secondary outcome measures examinedare CV complications at 28 days post randomization increase in cardiac injury marker (hs-Troponin) and change in inflammatory marker (TNF-alpha).

The study will be performing the following tests: ECG including QTc interval assessment, echocardiogram to measure left-ventricular ejection fraction (LVEF), chest X-ray, local laboratory (including CBC, AST/ALT, alkaline phosphatase, bilirubin, creatinine/eGFR, INR, pregnancy test (in women with child-bearing potential only), lymphocyte count and LDH. A C-SSRS. Frozen plasma will be retained for central analysis of CardiolRx™ levels, hs-Troponin, NT-proBNP, D-dimer as well as inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10).

We are highly confident that, due to the company's earlier results in administrating this treatment to mice and given the gene crossover characteristic of Cannabidiol, that the results will show improvement in the following metrics: BNP, Collagen, Fibrosis, Myocyte area, GAPDH, IL1, IL6, IL10, CD69 markers.

The company's time frame plans to complete the study in Q4 2021. With 422 patients being enrolled in this study, we expect the results to provide a clear indication on the outcome measured. Furthermore, Cardiol Therapeutics will gather a significant amount of data that will help the company further their understanding of the innerworkings of Cannabidiol within COVID-19 inflamed cardiovascular tissue and be beneficial in the development of their other treatments.

CardiolRx is poised to help with the present crisis and well positioned in the long term. However, it is imperative to keep in mind that before COVID-19, a global rise in diabetes, hypertensive blood pressure, and obesity led to an increase in heart failure. The wide spread of COVID-19 might even seem insignificant in the face of a market desperate for novel pharmaceutical treatments for heart failure. Moreover, if COVID-19 proves to be endemic, there will be a need for cardioprotective drugs for high-risk patients for many years to come.

2. Acute Myocarditis treatment

Myocarditis is an inflammatory disease of the heart muscle, the course of which is highly variable and depends on the cause and degree of inflammation. Myocarditis refers to acute or chronic inflammation of the heart muscle.

Acute Myocarditis is an uncommon form of cardiovascular illness that is characterized by sudden mortality, chest pain, and heart failure. Inflammation of the heart muscle (myocardium) is the most common cause, which often occurs after a viral infection. Most patients recover within seven days, however, in others, the inflammation continues and leads to heart failure. Acute Myocarditis is responsible for 0.5 to 3.5 percent of heart failure admissions to U.S. hospitals[29]. Most myocarditis instances are found in young adults, with males being affected more frequently than females. It remains the most prevalent cause of sudden cardiac death in persons under 35.

Given the high risk of heart failure associated with acute myocarditis, therapy includes drugs usually administered for heart failure. However, no known treatment exists for Acute Myocarditis. Some patients had positive results from using immunosuppressive drugs (azathioprine) in combination with steroids, or immune-modulation therapy using immune globulin. Nevertheless, the evidence is insufficient to accept either as a recommended treatment.

Given these facts, there is enough incentive, and a basis of experimental evidence demonstrating the anti-inflammatory activity of Cannabidiol in cardiovascular disease models to develop CardiolRx as a potential therapy for acute myocarditis.

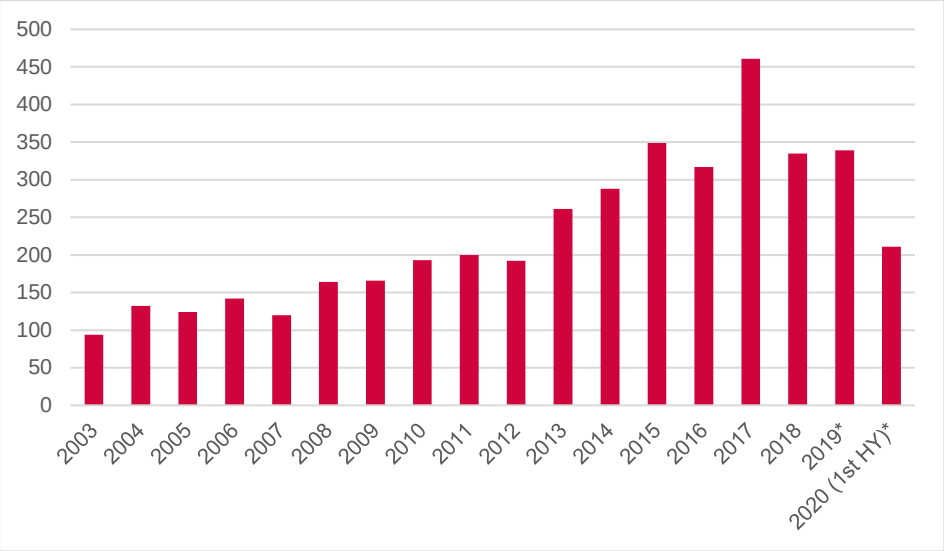
Based on the most recent data from the 'Global Burden of Disease Study,' myocarditis prevalence is estimated to be around 22 people per 100,000 accounting for a total of around 73,000 possible patients in the US alone. As there are currently no known treatments and fewer than 200,000 individuals affected by this disease, Cardiol Therapeutics could apply for the Orphan Drug designation in case of successful Phase III trials.

[29] https://rarediseases.org/rare-diseases/myocarditis/

2.1. Orphan Drug designation

In the United States, a specialized orphan drug designation is given to medications that are being developed to address medical problems affecting fewer than 200,000 individuals. Orphan illnesses are disorders for which no known treatment exists. Our research has indicated that 4088 Orphan drug designations have been approved by the FDA in the period between 2003 and today[30].

Number of orphan designations accepted in the U.S. 2003-2021



Sources: EvaluatePharma, GBC AG

For a drug to qualify for orphan designation both the drug and the disease or condition must meet certain criteria specified by the FDA (21 CFR Part 316). Rather than looking at the reasons why the FDA would approve a treatment, we investigated the reasons to determine the probability of refusal of the Orphan Drug designation in case of conclusive Phase III trials and assuming no administrative issues in the process.

Refusal to grant orphan-drug designation.
The FDA will refuse to grant a request for orphan-drug designation if any of the following reasons apply:

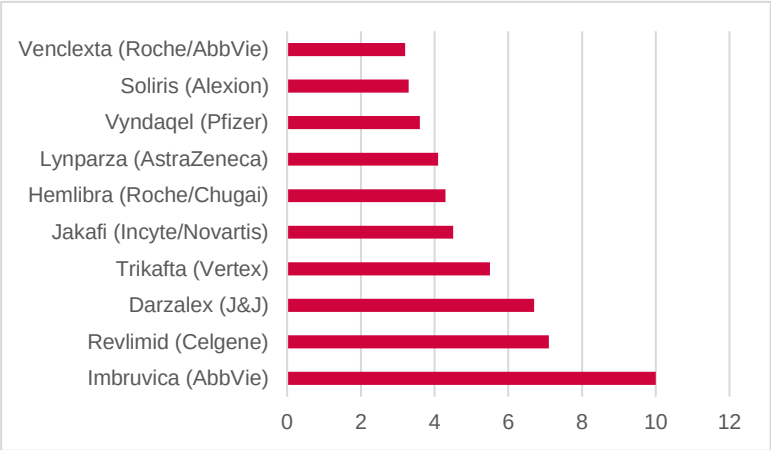
- insufficient evidence that the drug is intended for treatment, prevention or diagnosis of a disease or condition in fewer than 200,000 people in the United States.
- Insufficient information about the effectiveness of the drug.
- The drug is otherwise the same drug as an already approved drug for the same rare disease without explanation of the possible clinical superiority of the subsequent drug.
- The request for designation contains an untrue statement of material fact or omits material information.

The orphan designation gives the following main **benefits** to the drug maker:

- Seven-year market exclusivity from the date of orphan designation approval
- Eligibility for accelerated approval through the FDA
- Waiver of New Drug Application fee.

[30] EvaluatePharma Orphan Drug Report 2019 | Evaluate

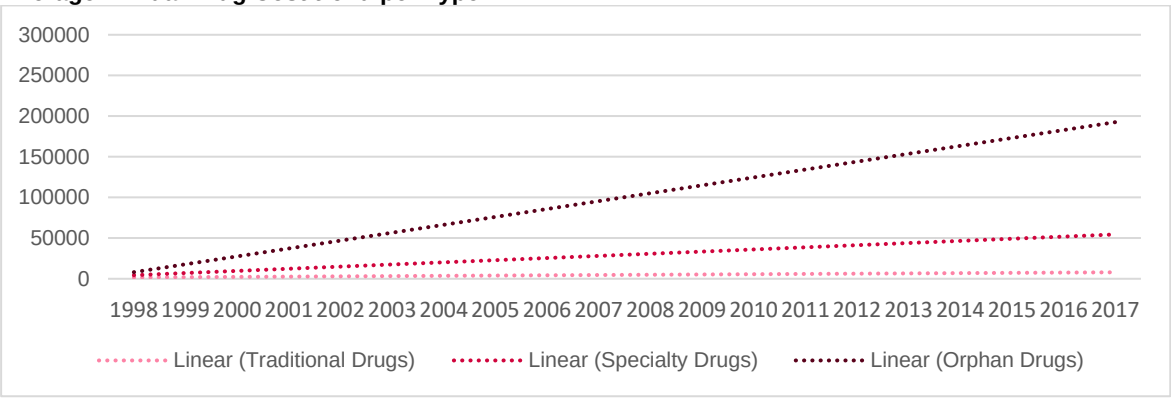
Projection of top 10 orphan drugs by global revenue 2025 in Mm USD



Sources: Statista, GBC AG

Another important advantage of obtaining the Orphan drug designation is the possible high market price, allowing the company to generate substantial margins. As shown below, the price difference between orphan drugs and traditional and specialized drugs has been greatly accelerating for the last three decades.

Average Annual Drug Cost trend per Type



Sources: Statista, GBC AG

2.2. A disease that carries a high cost

The Journal of American College of Cardiology published an article in 2019[31] providing insight into the costs of hospitalization for patients with Acute Myocarditis. They analyzed data from 2005 to 2014. Their findings are summarized in the following table:

Indicator	2005	2014	Change
Yearly acute myocarditis hospitalizations (AMH)	3,470	4,865	+40.20%
Mean length of stay (LOS)	7.4	7.4	0%
Mean Hospital Charges	USD68,849	USD 110,568	+60.59%
Discharged with home care services	6.5%	9.5%	+46.15%
Following complications			
Cardiac arrest	2.7%	4.6%	+70.37%

[31] J Am Coll Cardiol. 2019 Mar, 73 (9_Supplement_1) 935

Cardiogenic shock	7.5%	12.6%	+68%
Atrial fibrillation and atrial flutter	7.9%	10.2%	+29,11%
Acute myocardial infarction	9.7%	12%	+23,71%
Heart failure (predominantly Systolic dysfunction)	5.9%	32.5%	+550,84%
Inpatient mortality	6.3%	6.3%	+0%

Sources: Journal of the American College of Cardiology[32]

On average, patients stay at the hospital for 7,4 days before being discharged. However, subsequent complications have been massively increasing over this nine-year period which confirms our earlier findings that the initial costs of HF are important but when factoring in the ensuing complications, they represent a massive burden, reaching an average of over USD185,000.

Acute Myocarditis is challenging for both young and older patients. A clear increase in complications, medical care costs and incidence makes finding a treatment for this severe disease more than attractive for any major pharmaceutical company. Furthermore, given the potential orphan drug status, the price could be set remarkably high, with margins of over 95% and still represent massive savings for both the patients and the healthcare system. As seen earlier, the complications represent often more than the cost of the first hospitalization and necessitate important resources both in human resources and specialized equipment. A study in 2017 has compatibilized the intravenous medication used during the admission of 1145 total patients analyzed:

Variable	Total	Non-MCS	IABP	ECMO
Intravenous medications during the admission				
Dobutamine	32	23	58	54
Milrinone	3	0	3	15
Dopamine	49	37	73	88
Norepinephrine	21	10	40	61
Epinephrine	26	13	37	79
High dose of steroid	5	2	5	26
IVIG	2	1	2	11
Heparin	48	34	73	93
Enoxaparin	11	11	12	6
Oral medication for maintain usage				
ACEi/ARB	44	45	49	35
Beta blocker	33	33	39	27
Digoxin	18	17	24	19
K sparing diuretics	13	11	28	2
Statin	5	6	8	3
Antiplatelets	45	47	51	29

Source: International Journal of Medical Sciences[33]

As seen in the previous table, there is an important mix of medication administrated to the patients. Some of these drugs are very toxic to the human body and could cause important damage (ex: high dose of steroids).

In-Hospital complications

Variable	Number of events (%)		
	Non MCS (n = 851)	IABP (n = 99)	ECMO (n = 195)
ventricular tachycardia/ventricular fibrillation	50 (5.9)	12 (12.1)	34 (17.4)
High degree atrioventricular block	61 (7.2)	8 (8.1)	11 (5.6)

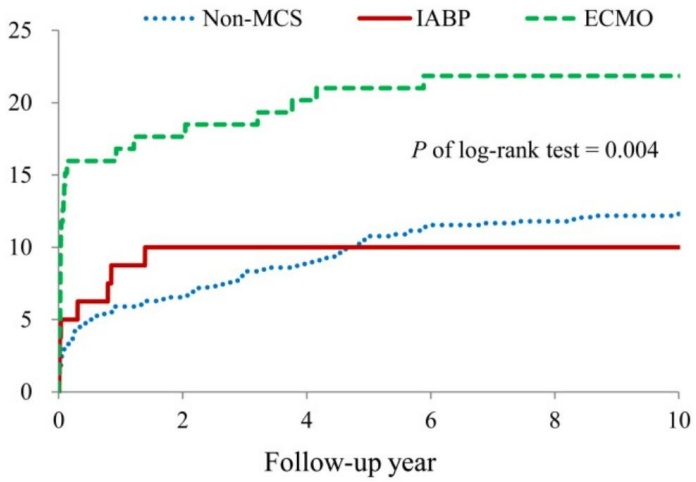
[32] https://www.jacc.org/doi/full/10.1016/S0735-1097%2819%2931542-6
[33] Heart Failure and Mortality of Adult Survivors from Acute Myocarditis Requiring Intensive Care Treatment - A Nationwide Cohort Study (nih.gov)

Acute renal failure	61 (7.2)	13 (13.1)	50 (25.6)
Need of hemodialysis	20 (2.4)	6 (6.1)	24 (12.3)
New onset of stroke	19 (2.2)	1 (1.0)	13 (6.7)
Pneumonia	114 (13.4)	12 (12.1)	24 (12.3)
Sepsis	115 (13.5)	24 (24.2)	36 (18.5)
In-hospital death	71 (8.3)	19 (19.2)	76 (39.0)

Source: International Journal of Medical science[34]

The important number of complications suffered by the hospitalized patients and more specifically, the number of in-hospital deaths clearly indicates the severity of this sickness. Additional analysis done by the same group of researchers indicates even more alarming mortality rates in subsequent years, reaching over 20% for patients that required extracorporeal membrane oxygenation (ECMO) support and a little over 10% for patients without any complications.

Cumulative incident of Cardiovascular death (%)



Source: International Journal of Medical Science[35]

Even if Acute Myocarditis is a rare disease affecting only 72,000 patients in the United States per year, the lack of both appropriate safe and effective treatment vectors and research during the past decades have led to alarming consequences. An increase in the number of complications in hospitals, a high mortality rate both during hospital admission and in the following year as well as increased costs of care for patients clearly call for a safe and effective treatment that is nontoxic for the human body.

2.3. Earlier research for CBD and Acute Myocarditis

In the search for a treatment of Acute Myocarditis, one promising avenue is the use of Cannabidiol. Extensive research has been conducted on the use of CBD against Acute Myocarditis but no important clinical trials, apart from the one anticipated by Cardiol Therapeutics, have been conducted on humans. CBD's therapeutic potential in a variety of cardiomyopathies has been investigated, ranging from repairing harm induced by a variety of cell stressors to reducing the occurrence of heart damage. These effects have been observed in a variety of models, including cells, tissues, and animals. An extensive review of the Cannabidiol effects on heart disease has been conducted in 2020.

[34] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5666557/
[35] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5666557/

Biological subject	CBD concentration	Experimental model	CBD treatment key results
In vitro models			
Human umbilical artery smooth muscle cells	0.1-10 μM	ROS modulation with NAC	Protective effect against aberrant proliferation and migration by an increased expression of HO-1
Human aortic endothelial cells	10 μM	High glucose/insulin	Decreased inflammatory (↓NF-$\kappa\beta$,) proliferation (↓JNK, ↓p70s6K), and increased survival (↑Akt) pathways
Human coronary artery endothelial cells	1.5, 3, 4.5, 6 μM	High glucose-induced endothelial cell inflammatory response	Reduced mitochondrial superoxide generation, NF-$\kappa\beta$ activation, and ICAM-1 and VCAM-1 expression
Primary human cardiomyocytes	4 μM	Diabetic cardiomyopathy by high glucose culture	Decrease of oxidative/nitrosative stress and NF-$\kappa\beta$ activation
Rat ventricular myocytes	1-10 μM	Normal conditions	Inhibition of L-type Ca^{2+} channels
Cardiomyocytes(iPSC)	1 μM	Ischemia/reperfusion and LPI administration	Reduced Ca^{2+} overload providing ischemia/reperfusion protection (↓GPR55 activation, ↓RhoA, ↓ROCK)
Ex vivo models			
Zucker diabetic rat aorta	10 μM	Diabetic cardiomyopathy	Improved acetylcholine-induced vasorelaxation
Rat mesenteric arteries	10 mg/kg	Diabetic cardiomyopathy	Endothelium COX- and NO-dependent enhanced vasorelaxation of Ach
Human mesenteric arteries	10 μM	Vasorelaxation	Promotes vasorelaxation via CB1 and the TRP activation and increased eNOS expression
Rat aorta	10 μM	Contraction stress by a combination of U46619 and methoxamine	Increase vasorelaxation of precontracted aorta by inhibition of calcium channels and increased transcriptional activity of PPARγ
In vivo models			
Primary and secondary hypertension rat model	10 mg/kg	Spontaneous and deoxycorticosterone acetate-salt hypertension	Reduction of cardiac and plasma oxidative stress (increased GSH and decreased GSSG) both in heart and plasma
Spontaneously hypertensive rats	3, 10 and 30 mg/kg	Hypertension	A dose-dependent decrease in HR and blood pressure mediated via TRPV1
In vivo rat I-R model	5 mg/kg	LAD ligation ischemia/reperfusion injury	A decrease in the infarct size and reduction of inflammation molecules like IL-6
In vivo I-R rabbit model	100 μg/kg	Acute reperfusion myocardial infarction	Reduced infarct size and facilitated restoration of left ventricular function
In vivo rat I-R model	10, 50 μg/kg	LAD ligation ischemia/reperfusion injury	Reduction of the infarct size and ventricular arrhythmias Inhibition of collagen-induced platelet aggregation
In vivo I-R rat model	50 μg/kg	LAD ligation ischemia/reperfusion -induced ventricular arrhythmias	Decreased incidence and duration of ventricular tachycardia and the total length of arrhythmias by activation of the adenosine receptor
Zucker diabetic rat	10 μM	Diabetic cardiomyopathy	Improvement on vasorelaxation by involvement of the CB_2 receptor and the enhancement of COX and SOD activity
Diabetic cardiomyopathy mice model	1, 10, 20 mg/kg	Streptozotocin induced diabetic cardiomyopathy	Attenuated myocardial dysfunction, cardiac fibrosis, oxidative/nitrosative stress, inflammation, and cell death
Autoimmune myocarditis mice model	**10 mg/kg**	**MyHC$\alpha_{334–352}$ induced autoimmune myocarditis**	**Attenuated the $CD3^+$ and $CD4^+$ T cell-mediated inflammatory response and injury, and myocardial fibrosis**
Doxorubicin-induced cardiomyopathy mice model	**5 mg/kg**	**Doxorubicin-induced cardiomyopathy**	**Decreased serum creatine kinase-MB, cTnT, cardiac malondialdehyde, TNF-α, NO and Ca^{2+} levels, increased glutathione, selenium, and zinc ions levels**
Doxorubicin-induced cardiomyopathy mice model	**10 mg/kg**	**Doxorubicin-induced cardiomyopathy**	**Attenuated oxidative and nitrative stress, improved mitochondrial function, and biogenesis**
In vivo rat stress model	1-72 mg/kg	Restraint stress	Abolished increase of HR and MAP by activation of 5-HT_{1A} receptor

Sources: Oxidative Medicine and Cellular longevity[36]

Out of this extensive list, one specific research is of particular interest. Observing the effects of CBD on MyHCα334–352 induced autoimmune myocarditis mice with a dosology of 10mg/kg, the authors have found that CBD attenuated the CD^{3+} and CD^{4+} T cell-mediated inflammatory response and injury, and myocardial fibrosis. This can be translated as saying that their results showed that CBD provides inflammatory and injury protection, acting as a cardioprotective element.

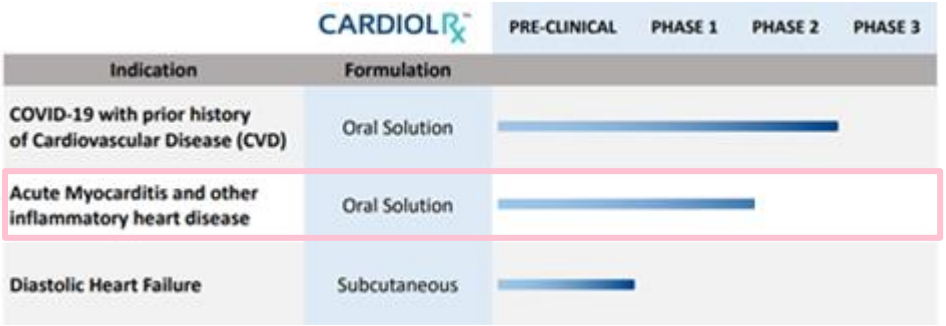
[36] https://doi.org/10.1155/2020/4587024

The main positive results for CBD against heart failure effects can be summarized as follow:

- Attenuates Inflammation in Induced (Experimental) Acute Myocarditis (EAM)
- Attenuates Inflammation-Associated Oxidative Stress Markers in EAM
- Protects against Fibrotic Remodeling of the Myocardium in EAM
- Attenuates Myocardial Dysfunction and Body Weight in EAM

2.4. Cardiol Rx against Acute Myocarditis

Cardiol Therapeutics is currently developing a treatment against Acute Myocarditis. The treatment is based on the use of high concentration of pure Cannabidiol.



Sources: Cardiol Therapeutics, GBC AG

Phase I trial confirms CardiolRx high dosage safety

The company has successfully completed their Phase I single and multiple ascending dose clinical trial for CardiolRx. The Phase I study was intended to examine CardiolRx's safety, tolerance, and pharmacokinetic profile at different levels of dosing. The study randomized 52 individuals from 25 to 60 years of age into two groups.

Group A had three subgroups with 12 participants, 9 of which received the drug and 3 received a placebo. Each dose was either 5 mg/kg or 15 mg/kg CardiolRx either fed or fasted. The two subgroups in Group B had 8 patients, 6 receiving the active ingredient and 2 a placebo. They each received, 5 mg/kg or 15 mg/kg twice a day for six days.

The Topline results showed that CardiolRx was safe and generally well tolerated with no significant harmful events or notable side effects observed in the experiment at all concentrations, even at the high dose of 2100mg per day. All protocol requirements were fulfilled by 51 out of 52 subjects.

After six days of dosage results showed no ECG or aberrant laboratory findings, in particular no liver enzyme elevations or negative signs with respect to cardiac rhythms. This is of the utmost significance for the company as they are working on this treatment for patients at high risk for cardiovascular disease. The adverse effects recorded were all moderate and mostly related to the gastrointestinal tract.

Pharmacokinetic tests have found that the medicine concentration usually increased in blood levels in relation to the dosage. The amount of exposure to the medicine after a single dosage of CardiolRx was six to seven times higher in the fed condition than the fasted state. The maximum quantity of CardiolRx in the blood levels was reached within 5 to 7 hours, with a half-life of 26 to 29 hours following single doses of CardiolRx in the fed condition.

The successful completion of the Phase I trial of CardiolRx serves as a foundation for the company’s future development. The company gained valuable insight not only regarding

the safety of the drug, but also how much of the drug is measured in the blood after administration, how the drug works in the body and the side effects associated with increased dosage. Even more, the trial revealed CardiolRx was well tolerated at all dose levels, with no serious adverse events. The company will be able to move on to the next phase of trials now that the safety of high dosage Cannabidiol is clearly assessed.

Phase II trial

Before starting Phase II trials, the company must first go through the Investigational New Drug Process (IND) with the FDA. In their IND application, drug developers must inform the FDA of the following elements: Animal study data and toxicity data (side effects that cause great harm), manufacturing information, clinical protocols (study plans) for studies to be conducted, data from any prior human research, information about the investigator. Cardiol has plans to file the IND application in Q3 2021.

The Phase II trial will be a multi-center, double-blind, randomized, placebo-controlled, parallel group designed study on the impact of CardiolRx™ on myocardial recovery. The trial has been planned and will be supervised by an independent Steering Committee that is made up of cardiology experts from Europe and North America.

The study is designed to look at the following elements:

Co-primary endpoints	Secondary endpoints
Left ventricular ejection fraction	Safety
Extracellular volume	Improvement in cardiac function
Global longitudinal strain	Improvement in quality of life

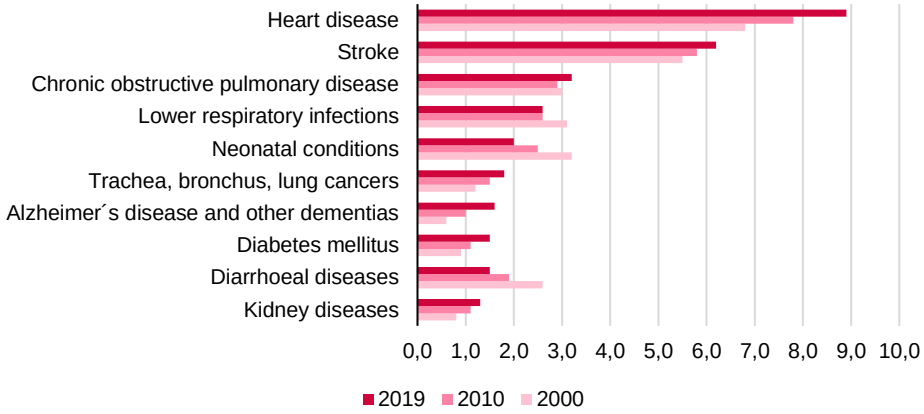
The study will enroll 100 patients in 15 to 20 sites across Canada, USA, and Europe, of which 50 will get CardiolRx and 50 a placebo. The treatment period is starting at 5 mg/kg of body weight/day to a maximum of 20 mg/kg/day administered twice a day with food. This is similar dosage as during Phase I and following the results from Phase I, it is administered in the most efficient way, with food.

Following the completion of the IND application in Q3 2021, clinical trials for Phase II testing will quickly commence, resulting in potential completion of the study by Q1 2023. Meanwhile, results from the Phase II/III clinical trials for CardiolRx COVID-19 will also increase the company's knowledge base on the workings of CBD on the heart and allow them to fine tune the Phase II trial for Acute Myocarditis.

3. Diastolic Heart Failure treatment

Cardiovascular disease remains one of the leading causes of death worldwide today. According to WHO statistics, 8.9 million patients died of heart disease in 2019, two million more than in 2000. Overall, is the leading cause of death, accounting for 9 percent of global deaths.

Leading causes of death globally



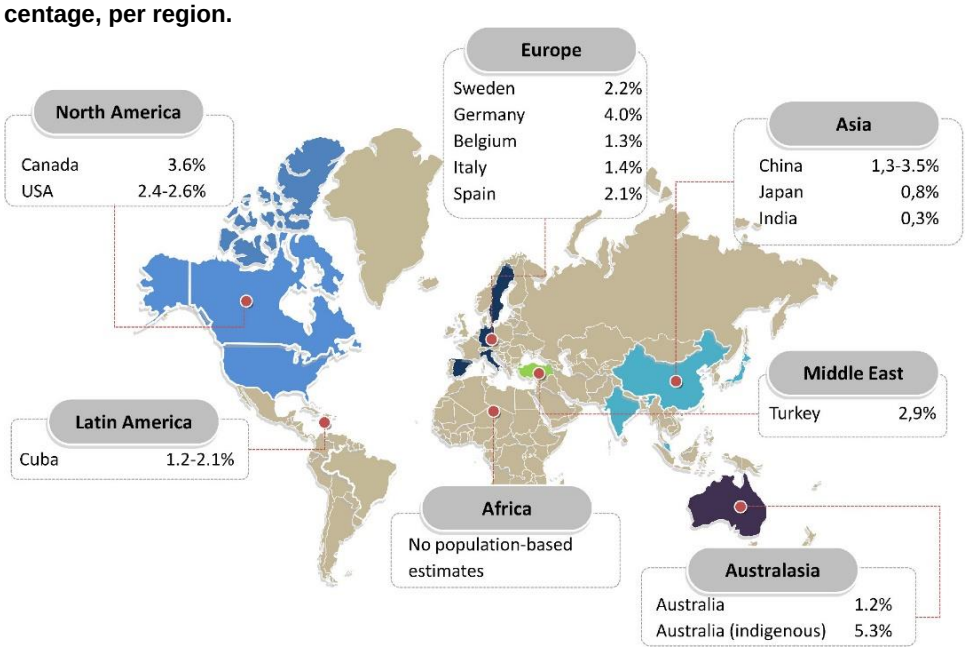
Sources: WHO, GBC AG

3.1. Heart Failure

The prevalence of chronic heart failure affects around 63 million people around the world. At the present time, approximately 6,2 million adults in Canada and the United States suffer from the disease and 379.800 people died in 2018[37]. In the U.S., the total cost of care (direct and indirect costs) in 2020 is estimated at $43.6 billion, with over 70% of costs attributed to medical costs. Without improvements in outcomes, the annual total cost of care is projected to increase to $69.7 billion by 2030[38].

[37] https://www.cdc.gov/heartdisease/heart_failure.htm
[38] https://doi.org/10.1161/HHF.0b013e318291329a.

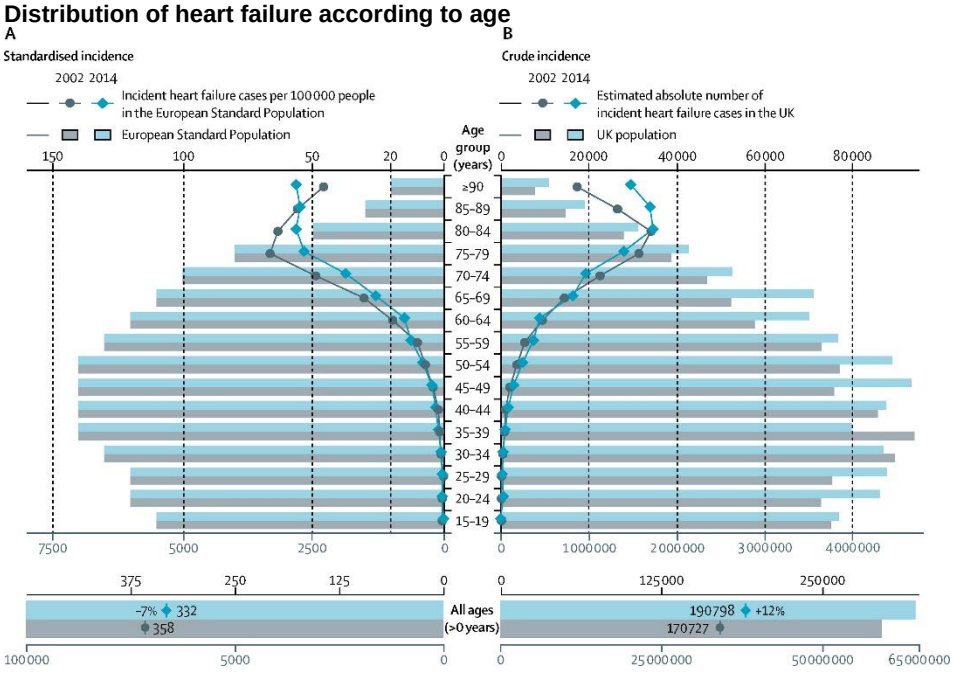
Prevalence of heart failure in population-based studies around the world, in percentage, per region.



Source: European Journal of Heart Failure[39]

Heart failure prevalence is not uniformly distributed but rather a spread as a function of age, comorbidities, ethnicity, sex, and many other factors.

Distribution of heart failure according to age



Source: The Lancet[40]

As seen in the previous graph, the high occurrence of heart failure is concentrated between the age of 50 and up, with a peak from 75 years on upwards.

[39] Epidemiology of heart failure - Groenewegen - 2020 - European Journal of Heart Failure - Wiley Online Library
[40] https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(17)32520-5.pdf

When looking at the U.S. population demographic, we can foresee this disease gaining heavy traction during the next 20 years as both the population over 50 years will grow and even more so the population of over 75 years old.

Source: CIA world facts

The total care costs of heart failure are particularly high and rising. As seen in the table underneath, these patients require highly skilled medical attention and equipment.

One-year outcome and rates of healthcare resource use according to group of diagnosis.

	Total	Never admitted due to HF	Remote HF hospitalization	Recent HF hospitalization	p-value
Mortality rate, n (%)	12,611 (14.3)	1,361 (11.3)	8,188 (13.0)	3,035 (23.7)	<0.001
Patients with an emergency department visit, n (%)	47,096 (53.4)	5,570 (44.9)	33,002 (52.4)	8,554 (66.8)	<0.001
Patients with unplanned HF hospital admission, n (%)	7,725 (8.8)	503 (4.1)	4,369 (6.9)	2,853 (22.3)	<0.001
Patients with unplanned all-cause hospital admission, n (%)	27,164 (30.8)	2,580 (20.8)	18,391 (29.2)	6,121 (47.8)	<0.001
Length of hospitalization, days (per admission), mean ± SD	4.1 ± 10.3	2.4 ± 7.5	3.8 ± 9.7	7.4 ± 13.8	<0.001
Patients with more than one hospital admission, n (%)	10,760 (12.2)	794 (6.4)	6,991 (11.1)	2,907 (22.7)	<0.001
Patients with more than 1 emergency department visit, n (%)	26,634 (30.2)	2,816 (22.7)	18,328 (29.1)	5,532 (43.2)	<0.001
Out-patient specialist contact (per patient)	5.0	3.9	5.1	5.7	<0.001
Primary care contact (per patient)	22.4	21.6	21.6	27.1	<0.001
Patients with use of skilled nursing facility, n (%)	11,377 (12.9)	1,241 (10.0)	7,495 (11.9)	2,650 (20.7)	<0.001

HF: heart failure; SD: standard deviation

Source: National library of Medicine[41]

The table below shows that heart failure is more likely to happen when comorbidities are present. On average, heart failure patients present over 5 comorbidities, the most frequent being hypertension, ischemic heart disease, atrial fibrillation, and diabetes mellitus.

[41] https://pubmed.ncbi.nlm.nih.gov/28235067/

Baseline characteristics according to group of diagnosis

	Total	Never admitted due to HF	Remote HF hospitalization	Recent HF hospitalization	p-value
Cases	88,195	12,407	62,982	12,806	
Age, years, mean ± SD	77.4 ± 12.0	79.9 ± 10.5	76.6 ± 12.4	79.0 ± 10.6	<0.001
Female, n (%)	48,320 (54.8)	8,173 (65,9)	33,026 (52.4)	8,173 (55.6)	<0.001
Number of comorbidities, mean ± SD	5.7 ± 2.0	5.1 ± 2.0	5.7 ± 2.0	6.4 ± 2.0	<0.001
Hypertension, n (%)	85,803 (97.3)	12,407 (100.0)	60,659 (96.3)	12,737 (99.5)	<0.001
Ischemic heart disease, n (%)	42,215 (47.9)	4,375 (35.3)	31,065 (49.3)	6,775 (52.9)	<0.001
Atrial fibrillation, n (%)	41,950 (47.6)	4,464 (36.0)	29,639 (47.1)	7,847 (61.3)	<0.001
Diabetes mellitus, n (%)	37,188 (42.2)	4,259 (34.3)	26,613 (42.3)	6,316 (49.3)	<0.001
Anemia, n (%)	29,429 (33.4)	2,521 (20.3)	21,235 (33.7)	5,673 (44.3)	<0.001
COPD, n (%)	28,612 (32.4)	2,802 (22.6)	20,920 (33.2)	4,890 (38.2)	<0.001
Valve heart disease, n (%)	28,263 (32.0)	1,539 (12.4)	21,074 (33.5)	5,650 (44.1)	<0.001
Chronic kidney disease, n (%)	25,974 (29.5)	2,447 (19.7)	18,207 (28.9)	5,320 (41.5)	<0.001
Depression, n (%)	23,043 (26.1)	3,235 (26.1)	16,202 (25.7)	3,606 (28.2)	<0.001
Cardiac conduction disorders, n (%)	19,865 (22.5)	1,290 (10.4)	14,633 (23.2)	3,942 (30.8)	<0.001
Cancer, n (%)	18,545 (21.0)	2,196 (17.7)	13,506 (21.4)	2,843 (22.2)	<0.001
Stroke, n (%)	16,127 (18.3)	1,776 (14.3)	11,802 (18.7)	2,549 (19.9)	<0.001
Previous acute myocardial infarction, n (%)	13,254 (15.0)	887 (7.1)	10,510 (16.7)	1,857 (14.5)	<0.001
Dementia, n (%)	10,257 (11.6)	1,470 (11.8)	7,179 (11.4)	1,608 (12.6)	<0.001
Cirrhosis, n (%)	2,416 (2.7)	244 (2,0)	1,718 (2.7)	454 (3.5)	<0.001

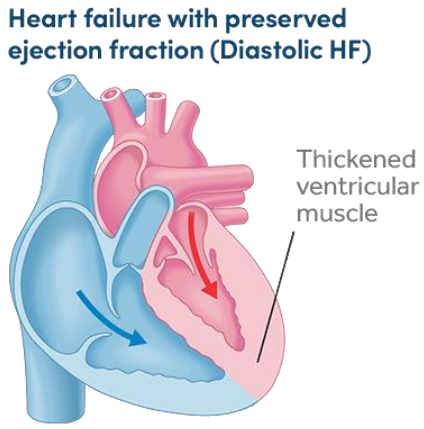
HF: heart failure; COPD: chronic obstructive pulmonary disease; SD: standard deviation

Source: National library of Medicine[42]

The most common cause of heart failure is when the heart can no longer pump the blood quantity that is necessary for the body's demands. Many people with HF exhibit shortness of breath, high heart rate, edema, impaired exercise capacity, and may have a variety of symptoms that can be challenging to manage daily. It is not uncommon for patients to be hospitalized for these symptoms, and in many cases these symptoms greatly degrade the quality of life.

3.2. Diastolic Heart Failure

There are two types of HF: one with a reduction of ejection fraction (the force with which blood gets ejected by the heart) called systolic failure and one with preserved ejection fraction (HFpEF) called diastolic failure. Diastolic heart failure, the disease targeted by Cardiol Therapeutics' treatment represents around 50% of all heart failure cases.



Source: Cardiol Therapeutics

[42] https://pubmed.ncbi.nlm.nih.gov/28235067/

Diastolic heart failure consists of the left ventricle losing its ability to relax normally due to tissue rigidity causing the heart to not properly fill with blood during the resting period between each beat. This results in pressure beginning to increase in the left heart chamber and the lungs.

Apart from tissue rigidity, there are two other causes for HFpEF. The decrease in sarcoplasmic/endoplasmic reticulum calcium ATPase pump (SERCA) responsible for the relaxation of the ventricular muscle and the presence of myocyte hypertrophy cardiomyopathies and hypothyroidism.

3.3. Current treatments against Diastolic heart failure

Clinical trials of pharmacological therapy for HFpEF have produced largely neutral results and there have been no significant treatment advances for Diastolic HF in over 20 years. Additionally, the treatments used have proven not effective for Diastolic heart failure. Therefore, the disease is not currently treated directly but rather the associated conditions such as hypertension, atrial fibrillation, or its symptoms such as edema.

The main objective of the drugs used in patient treatments is to control the systolic and diastolic hypertension and use diuretics to relieve the water accumulated in the lungs. Moreover, an effective treatment of the disease would further impact the following conditions resulting from HFpEF: Hypertension, Atrial fibrillation, Myocardial ischemia, Hyperlipidemia. It is also of the upmost importance that the medication does not cause the following precipitant conditions: tachycardia, abrupt severe elevations in systemic blood pressure, ischemia, and AF. The following table shows which treatments are currently in use and what are their advantages and shortcomings.

Current treatment for DHF and their efficiency

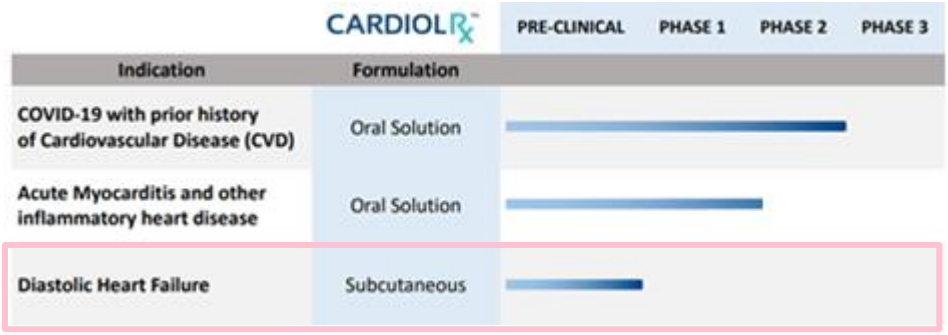
Treatment	Name	Summary	Comments
Mineralocorticoid receptor antagonists	Spironolactone	Primary outcome was not statistically different	The spironolactone group had twice the rate of hyperkalemia (18.7 versus 9.1 percent) and also a higher rate of increased serum creatinine
Angiotensin receptor-neprilysin inhibitor	Sacubitril-Valsartan	The frequency of the primary composite outcome of total hospitalizations for HF and death from cardiovascular causes was not significantly lower with Sacubitril-Valsartan	Reserved for patients already taking Spironolactone
ACE inhibitors	Perindopril	There is no evidence that the drug directly improves overall morbidity or mortality in patients	ACE inhibitors play an important role in the treatment of the disease processes that contribute to the development of HFpEF
Angiotensin II receptor blockers	Candesartan	There is no evidence from randomized clinical studies that ARB therapy directly improves overall morbidity or mortality in patients with HFpEF. There is no evidence of improved diastolic function with ARB treatment as compared with other therapies in patients with asymptomatic LV diastolic dysfunction or overt HFpEF	At a mean follow-up of 49.5 months, there was no significant difference in the primary end point of death from any cause or hospitalization for a cardiovascular cause
Diuretics	CHAMPION	These drugs treat volume overload (e.g. of water in the lungs)	Administered with caution to avoid excessive preload reduction and hypotension

Calcium channel blockers	Calcium channel blockers	Calcium channel blockers may be useful in the treatment of hypertension in patients with HFpEF, though the evidence is very limited	More research is necessary to assess their true potential
Beta blockers	Beta-blockers	There was no consistent benefit from beta blockers among patients with AF	Usage not recommended in the absence of an alternative indication, such as angina

Sources: UpToDate[43], GBC AG

As clearly demonstrated in the previous table, there is an urgent need to find a reliable and effective treatment against Diastolic HF as diuretics remain the most common way to treat this disease. Cardiol Therapeutics is currently developing a new formulation for their CardiolRx drug in association with the TecSalud del Tecnológico de Monterrey and DeBakey Heart & Vascular Center.

3.4. Subcutaneous Cannabidiol Formulation



Sources: Cardiol Therapeutics, GBC AG

Supported by all the previously discussed advantages of Cannabidiol, Cardiol Therapeutics is now focusing on a new way to administer their drug to increase its bioavailability in the blood compared to the current oral formulation. The objective is to alleviate cardiac inflammation and to reduce fibrosis with a dosage form that gives more predictable pharmacokinetics than can be achieved orally. By preventing fibrosis, the Cardiol Therapeutics could help reduce not only the HEpEF occurrence but maybe also reduce the percentage of second occurrence following heart failure.

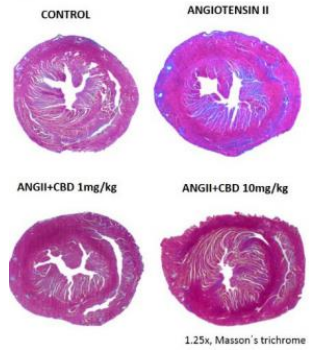
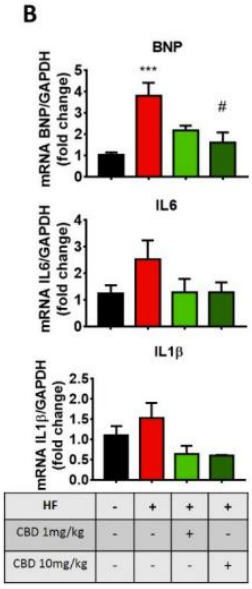
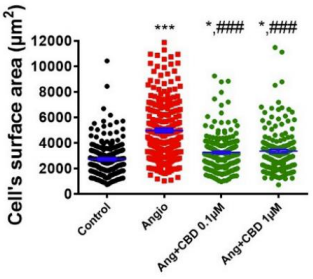
Two new studies performed by a third party were published in May 2020:

1. Cardioprotective effect of Cannabidiol in a non-ischemic model of heart failure
2. Nano-encapsulated cyclosporine-A attenuates the cardiac inflammation and mitochondrial dysfunction in a non-ischemic model of cardiomyopathy.

[43] Treatment and prognosis of heart failure with preserved ejection fraction - UpToDate

The results are as following:

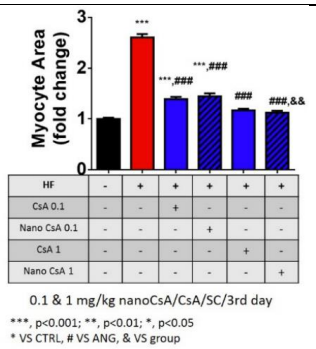
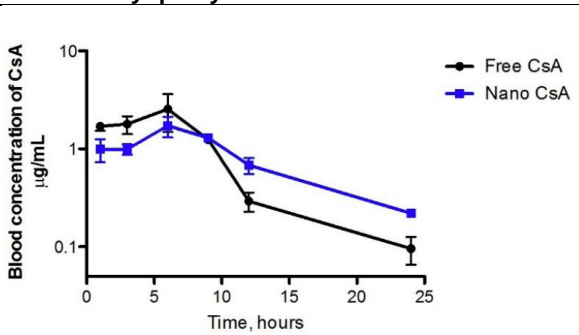
1 - Cardioprotective effect of Cannabidiol in a non-ischemic model of heart failure

		
CBD attenuating fibrosis in this model of non-ischemic cardiomyopathy	Attenuation of myocyte hypertrophy, and attenuated tissue expression of BNP, collagen 1, IL1β and IL6	CBD attenuated the hypertrophic effects of Angiotensin II, resulting in cell area size comparable to control

Source: JACC.org[44]

These results are very promising as the researchers concluded that their *findings support the role of CBD as a cardioprotective therapy in chronic HF. The potential mechanisms involve several pathways of proliferation and survival leading to an anti-inflammatory and anti-hypertrophic phenotype*[3].

2 - Nano encapsulated cyclosporine-A attenuates the cardiac inflammation and mitochondrial dysfunction in a non-ischemic model of cardiomyopathy

Results		
Description	A dose-dependent anti-hypertrophic effect was observed in both free and Nano CsA	Biodistribution showed decreased Nano CsA levels in plasma

Source: JACC.org45

[44] https://www.jacc.org/doi/full/10.1016/S0735-1097%2820%2931332-2
[45] doi: 10.1016/S0735-1097(20)31331-0

Additionally, to the results described above, the second study shows no differences regarding complete blood counts between free and Nano cyclosporin A (CsA). CsA and Nano CsA demonstrate a trend in decreased inflammatory serum cytokines. Preliminary results show decreased levels of blood urea nitrogen (BUN) and serum creatinine when CsA is nano encapsulated. The authors conclude as follows: *Free CsA and Nano CsA show a similar therapeutic potential for HF, but Nano CsA is present longer in blood circulation and could decrease nephrotoxicity*[46].

Relying on the known cardioprotective and fibrosis-reducing properties of Cannabidiol previously discussed and following these promising results, Cardiol Therapeutics will be injecting significant amounts of cash in 2021 and 2022 into the R&D of CardiolRx as a treatment for Diastolic HF. This will allow the company to achieve progress in the further understanding of both Cannabidiol and the subcutaneous delivery mechanism. This delivery method prevents first-pass metabolism, and therefore, maximizes and maintains blood levels allowing the drug to target more accurately and efficiently inflammation and increased fibrosis in the heart.

[46] doi: 10.1016/S0735-1097(20)31331-0

COMPANY PERFORMANCE AND FORECAST

1. Current Financial Situation

P&L in Mio. CAD	FY 2019	FY 2020	FY 2021e
R&D	3,53	10,515	12
Salaries	1,834	2,086	2,6
Cash	6,956	14,0	25
Net profits	-13,684	-20,64	-18,41

Sources: Cardiol Therapeutics, GBC AG

For the year ending on 31 December 2020, costs for research and development climbed to 10,5M CAD, up from 3,5M CAD in the year ending on 31 December 2019, an increase of almost 300% YoY. The main reason for this is that the company completed its Health Canada approved Phase I clinical study of CardiolRx Acute Myocarditis and appointed Worldwide Clinical Trials as contract research organization (CRO) for the Company's Phase II/III Outcomes Trial in High-risk Patients Hospitalized with COVID-19.

In addition, the company had to take an accounting charge of 5.4M CAD in inventory in Q4 2020. Given the aim of the company is to utilize this entirely for future clinical programs and research and development, the inventory had to be immediately charged even if the bulk of the inventory is still available for future periods.

Cardiol Therapeutics is currently in a R&D stage and producing no revenues, so it should come as no surprise that they run losses for some years until the commercialization of one of their treatments. Therefore, the company still requires important funding to pursue their operations.

In 2020, the company raised 17,25M CAD and over 22M CAD in 2021. They also received proceeds of over 11,07M CAD from the exercise of warrants. In total, during the past 18 months, the company has received over to 50M CAD.

We estimate the company's losses for FY 2021e to reach 19,15M CAD, with no revenues while retaining a cash reserve of over 10M CAD for YE 2021e. These estimates will be updated with every quarterly results.

The prospectus filed by the company for each of their capital raises gives a great insight into expenses to come in the next years and the company's future products.

Use of Proceeds (Corporation prospectus 2018 to Dec. 2020) In CAD	Amount	Spent	Remaining
Cardiol CTX product series and acute myocarditis: Basic science, pre-clinical studies, and a Phase I clinical program	1,700,000	1,700,000	-

Use of Proceeds (Prospectus May 2020 to December 2020) In CAD	Amount	Spent	Remaining
Clinical Trials (Phase I and Phase II/III)	6,400,000	1,172,184	5,227,816
Pre-clinical studies	900,000	180,550	719,450
Product Development	**1,100,000**	**44,896**	1,055,104

The prospectus filed by the company for their last capital raise of over 22M CAD gives a clear description of how the proceeds will be used, and we are pleased to find that more than 57% of the money raised is directed at R&D purposes.

Planned Use of proceeds in CAD	Approximate Use of Net Proceeds
Phase II/III clinical trials in acute myocarditis	$6,500,000
Pre-clinical studies	1,500,000
Research and development of subcutaneous formulation	4,000,000
General and administrative expenses, working capital and other general corporate expenses	8,983,010
TOTAL:	$20,983,010

The company's R&D focus for the next 24 months should include the Phase II/III clinical trials for Acute Myocarditis and the development, pre-clinical studies and a Phase I clinical trial of their proprietary subcutaneous formulation that would be used for the mass market treatment of Diastolic Heart Failure.

Given the above, we believe the current financial state of the company to be extremely healthy. Cardiol Therapeutics has an important cash position and a clear planification of expenses that will allow advancing current programs and maintaining a healthy pipeline of complementary products.

2. Forecast and Model Assumptions

In the pharmaceutical world, few companies have only one product in two formulations, tackling and treating the same symptoms for three specifically different markets. Cardiol Therapeutics, with their CardiolRx formulation answers to this premise. Consequently, the results of their Phase II/III COVID-19 trials will be decisive for the company's future. We expect these trials to provide significant positive results that will be leveraged for all other treatments.

The company model also hints at a high risk/high reward investment strategy for investors. However, as we discussed throughout our report, we believe the risk of CardiolRx not obtaining FDA approval highly unlikely due to previous scientific research. We estimate the company to be low risk/high reward and have an exceedingly high likelihood of commercializing at least one if not all three different treatments against heart inflammation diseases. Our DCF model is based upon this assertion.

It is important to point out that despite our favorable forecast, we believe the most likely future scenario for the company to be a takeover either after the FDA EUA approval for the COVID-19 treatment or latest after the FDA approval for the Acute Myocarditis treatment.

2.1. Forecast basis – Cardiol COVID-19

Current ongoing phase:

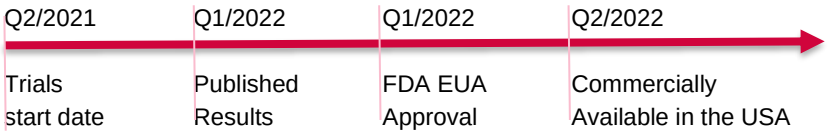
Title	Status	Phases	Start Date	Primary Completion Date	Completion Date
Cannabidiol in patients with COVID-19 and cardiovascular disease or risk factors	Recruiting	Phase II/ Phase III	30/04/2021	01/11/2021	01/12/2021

Sources: Clinicaltrials.gov, GBC AG

The current ongoing multi-center, double-blind, placebo-controlled trial is designed to evaluate the efficacy and safety of CardiolRx in patients with COVID-19 and cardiovascular disease or risk factors. We believe enrolment completion to happen very rapidly and the trials to be conducted and finalized within the next 6 months. Following the completion date, we believe results could be published within the following two months.

Our estimated timeline is subject to rapid enrolment of patients. This can turn out to be a difficult task as the population at risk is prioritized in vaccination campaigns. However, even if vaccination is progressing well in the United States and Europe, available data suggests that there are opportunities in other countries to keep the schedule on track. In that regard, we would expect the company to announce partnership from their CRO with countries that are currently having difficulties.

Estimated timeline to commercialization:



Once the results are published, we expect EUA approval from the FDA to be received within the following month as a proven effective treatment is urgently needed to help COVID positive patients during the acute phase of the infection.

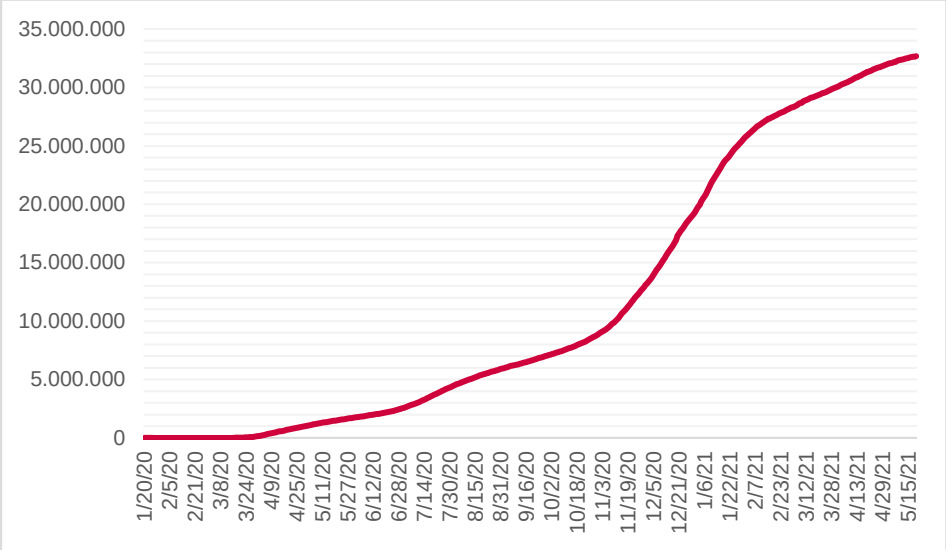
Estimated Revenues

The current pandemic has proven to be extremely complicated to predict. Estimating the revenues Cardiol Therapeutics can generate from their treatment is not an easy task. We expect, following the successful commercialization latest April 2022, the company to start generating revenues very rapidly. The key element for a successful international launch is not only having a proven drug but relying on a team of experienced and qualified specialists. In that regard, we believe the company's management team to be a group of highly skilled and competent individuals that combine all the necessary experience to successfully complete the takeoff of CardiolRx COVID-19. Additionally, the team has commercialized Cortalex in pharmacies throughout Canada, a complex and competitive environment.

Given that we expect the manufacturing costs for CardiolRx for COVID-19 to be incredibly low and the company's expenses would be largely reduced compared to any roll-out of new drugs, we expect the company to generate net margins of close to 85% for this medication. If it works, the company will have truly little campaigning and publicity to do, as the demand will come directly from health insurance companies and even patients.

As for the number of potential patients, we evaluate this to be around 200,000 people worldwide during 2022. This number is depending on new variants, as well as the situation in countries such as Brazil and India in less than 12 months from now.

The cumulative hospitalization data in the United States starts showing signs of capping that corresponds to the mass vaccination effort and the end of the 3rd wave.



Source: CDC[47], GBC AG

Additionally, new treatments are currently in development from competitors. Two projects are nearing completion, currently ongoing in Phase III trials.

The first, Molnupiravir, is a collaboration between the American pharmaceutical corporation Merck and the biotechnology company Ridgeback Biotherapeutics. It was originally created to treat the flu but has now been modified such that it may be taken as a pill against the Corona virus. The treatment consists in taking one pill twice a day.

Preliminary results shows that the treatment has been well tolerated by the few hundred persons who have taken it so far. The virus was no longer detectable after 5 days for all individuals treated with Molnupiravir, although it was still present in 26% of the placebo group. Additional findings are expected in the fall.

The second study is being undertaken by the Swiss pharmaceutical company Roche in collaboration with the American company Atea Pharmaceuticals. The AT-527 treatment is being evaluated in over 1,400 volunteers in Europe and Japan, some of whom are as young as 12 years old. The company has indicated that they expect commercialization as early as 2022. The results are not yet available.

These two possible treatments pose a real threat to the market share of CardiolRx. These drugs could be available in pharmacies and taken directly by the patient at home.

Considering these two competitors, and the improving COVID-19 situation, we prefer to apply a very conservative scenario when looking at future revenues from the CardiolRx treatment against COVID-19. We believe that the true value of this treatment is the accelerated Phase II/III trials and how the company can monetize the results obtained to drive the development of their other treatments.

Revenue assumptions	FY22e	FY23e	FY24e
Total Market Size (# Potential Patients)	133.912	67.311	–
Average # of Patients per Year	6.696	13.462	–
% Of Market on Medication	5,0	20,0	–
Annual Price Per Patient ($ CAD)	2.000	2.000	2.000

[47] https://gis.cdc.gov/grasp/covidnet/COVID19_3.html

Covid-19 - Revenue ($ CAD)	13.000.000	26.900.000	–

Revenues

CardiolRx – COVID-19 estimates

P&L in Mio. CAD	FY 2022e	FY 2023e	FY 2024e
Revenues	25	15	0
Net profits	16	10	0

Even though we do not consider this treatment core to Cardiol Therapeutics' future revenues, it is key in generating large sums of net profit within a noticeably short period of time as well as gaining recognition for their CardiolRx product on an international level.

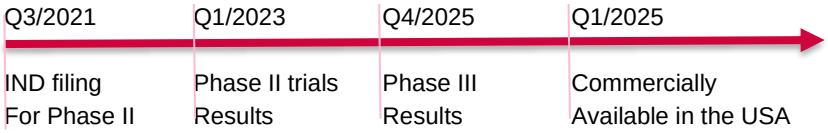
We believe that the commercialization of this treatment could help the company limit additional dilution by providing cash flow in the short term and increase shareholder value substantially on the long term.

Furthermore, the ongoing trials, if proven successful, will considerably de-risk the development of their treatment against Acute Myocarditis and their following injectable diastolic HF treatment.

2.2. Forecast basis – CardiolRx Acute Myocarditis

Cardiol Therapeutics IND application for Phase II trials should be authorized in the second half of 2021. We expect the trials to begin within the following 90 days and patient enrollment to take 18 months. Even if this is a well-known disease with frequent cases, there is a long list of patient conditions exclusion in the Phase II planned trial, that we believe will result in a slower enrollment process.

Estimated timeline to commercialization:



Upon successful completion of the Phase II trials, the company will have to submit a Phase II/III application and upon acceptance, conduct the corresponding trials. We believe that in an optimistic scenario, commercialization could happen in the USA in Q1 2025.

Pricing

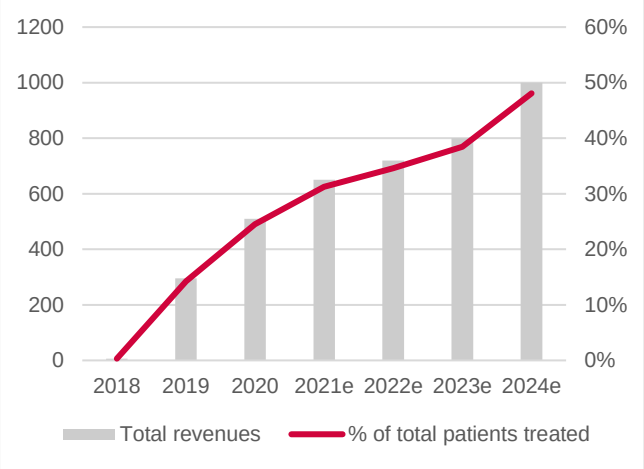
As there is no current approved drug for this disease, let alone efficient medication, we based our estimates on the possible savings for insurance companies and patients of the total cost of care. We took the cost of hospitalization without complications as a maximum for the treatment price. These costs average around 14,000 USD as previously discussed. We believe that there should be an important incentive for insurance companies to approve the use of this drug both due to its effectiveness and due to important savings realized.

Combining these two key elements will increase the approval rate and pre-acceptance rate of the treatment with insurance companies. These two factors will have a critical impact on the adoption rate of the treatment. Therefore, we established the drug price at 3,000 CAD. As we are still waiting for Phase II trials to commence, we prefer keeping very

conservative estimates. We believe this to be the lowest starting price and, given the evolution of the market until FDA approval, we could revise our estimation upwards.

Revenues
To estimate the revenue generated from the Acute Myocarditis treatment, we established the Epidiolex® adoption rate as a comparison.

Epidiolex® sales figures in USD and % of total patients treated



Sources: GW Pharmaceuticals, GBC AG

As seen in the graph above, the adoption of this medication is extremely fast, even at the high price of $41,000 CAD before discounts and rebates for a yearly treatment. In the case of an Epidiolex® treatment, health insurance companies in the US have an acceptance of over 97%, with 63% preapproving the treatment[48].

We believe that Cardiol Pharmaceutics could sustain the same acceptance rate and even higher preapproval as the potential savings are colossal for health insurance companies and patients and the price of the drug being more than 10x lower. Taking all the above factors into account, we project the following sales and revenues for CardiolRx as a treatment for Acute Myocarditis:

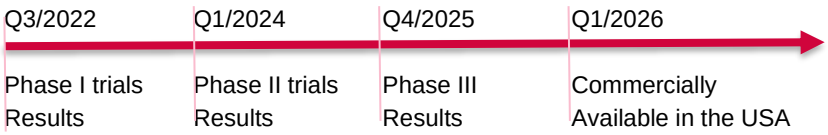
Revenue assumptions	FY25e	FY26e	FY27e	FY28e	FY29e	FY30e
US Population / 2027 including Europe	340.130.652	341.933.344	707.802.022	711.553.373	715.324.606	719.115.826
Total Market Size (# Potential Patients)	74.829	75.225	155.716	156.542	157.371	158.205
Average # of Patients per Year	3.741	7.523	38.929	46.963	62.949	79.103
% Of Market on Medication	5,0	10,0	25,0	30,0	40,0	50,0
Growth Rate in # of patients		101,1	417,5	20,0	34,0	25,7
Annual Price Per Patient ($ CAD)	3.000	3.000	3.000	3.000	3.000	3.000
Acute Myocarditis - Revenue ($ CAD)	11.200.000	22.600.000	116.800.000	140.900.000	188.800.000	237.300.000
Annual Growth Rate (%)		101,1	417,5	20,6	34,0	25,7

2.3. Forecast basis – Diastolic Heart failure treatment

Diastolic Heart Failure is a common disease. We believe that the Phase II and Phase III results would be obtained relatively fast as the enrolment will not prove challenging.

[48] https://ir.gwpharm.com/static-files/1b983943-92da-4e39-8385-02e23fa71bfd

Additionally, the company will be counting on the research and experience from both Phase II/II COVID-19 treatment and Acute Myocarditis.
Estimated timeline to commercialization:



The number of possible patients for diastolic heart failure is well documented. In the U.S. only, around 275,000 new cases are diagnosed every year. The total amount of people suffering from this disease is currently around 3,25M[49].

As discussed previously, this disease does not have an effective treatment and just as for the Acute Myocarditis, it results in costly hospitalization that run cost on average of over 14.000 CAD. Following the same argument as before, we established the price of this treatment at 4.500 CAD.

Revenue assumptions	FY26e	FY27e	FY28e	FY29e	FY30e
US Population / 2028 including Europe	340.130.652	341.933.344	707.802.022	711.553.373	715.324.606
Total Market Size (# Potential Patients)	275.000	275.000	550.000	550.000	16.850.000
Average # of Patients per Year	5.000	25.000	100.000	150.000	210,625
Annual Price Per Patient ($ CAD)	4.500	4.500	4.500	4.500	4.500
Diastolic Heart Failure - Revenue ($ CAD)	22.500.000	112.500.000	450.000.000	675.000.000	947.800.000
Annual Growth Rate (%)		400	300	50	40

2.4. Forecast basis – Cortalex

The company has successfully developed Cortalex and commercialized it in Canada. Cortalex, the retail version of the CardiolRx product, is a high concentration, high purity oil based oral Cannabidiol product. The current price of the product is 200 CAD per bottle. Pediatric patients can obtain a 40% discount on the price. The product is available across Canada exclusively at Medical Cannabis by Shoppers™ online portal, a subsidiary of Shoppers Drug Mart Inc.

Our estimated revenues are negligeable as we do not expect the company to achieve meaningful commercial success with this product. Cannabidiol formulations are operating in a highly competitive and restrictive environment. The Canadian market is already saturated, even for prescription drugs.

CBD products are legally viewed as cannabis products in Canada and therefore highly regulated. Minimal marketing can be done, no medical claims can be made, and the product label must include most of the same warnings as THC products. We, therefore, believe the environment to not be right at the current time to allow Cortalex sales to pick up again.

In this regard, the University of Ottawa has released an important consultation document, entitled *Assessing the Economic Impact of Regulating CBD Products as Health Products*. They argue that the law currently does not distinguish CBD from other cannabis products

[49] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5494150/

and Canada should regulate CBD products as natural health products rather than cannabis products.

In the long term, the success of Cardiol´s other treatments could help the sales for this product. However, if no medical claim can be made for this product, its reach will be limited.

We still value Cortalex but argue that the current state of legislation in Canada does not allow the company to market, publicize, and develop this product in any meaningful way resulting in customers having to find and get to know this product by themselves.

If such changes would be made to the Canadian *Cannabis Act,* we would review our estimates upwards for this product in a significant way as it still carries the advantage of being the purest high concentrate CBD medication available on the market that is pharmaceutically produced.

Revenue assumptions	**FY21**e	**FY22**e	**FY23**e
Cortalex - Revenue ($ CAD)	250.000	400.000	550.000

3. Sales and earnings forecasts

Our forecasts are based on the previously detailed performance and timeline for each of the three treatments currently in development for the company and the already commercially available product, Cortalex.

In order to give the company a fair earnings forecast, we are looking at the revenues for the next 10 years. The company is currently working on groundbreaking treatments for diseases facing scarcity in both treatment availability and efficiency.

We estimate that the company revenues, based on a full-scale development, without any royalty business model included, could reach over 2.982M CAD during the period 2021e-2030e. The foundation of this scenario is the FDA approval of all treatments within our expected timeline. We consider our estimates to be very conservative relative to this scenario.

Company revenue estimates for the period 2021-2030 (in M CAD)

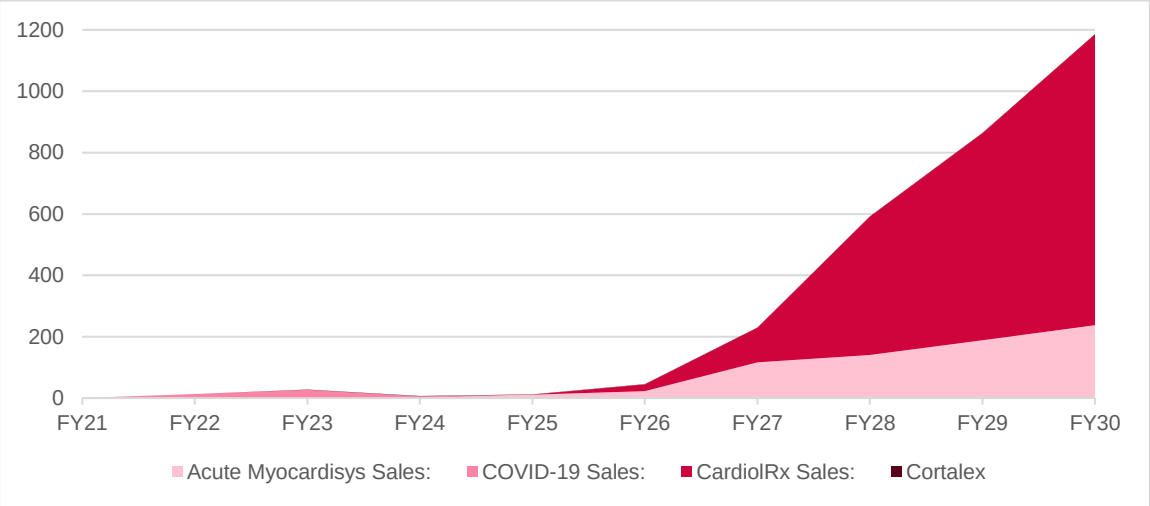
	FY21e	FY22e	FY23e	FY24e	FY25e	FY26e	FY27e	FY28e	FY29e	FY30e
Total Revenue:	-	13,4	26,9	6,2	11,2	45,1	229,3	590,9	867,8	1.191,1

Source: GBC AG

As a comparative, Epidiolex®, the star treatment from Jazz Pharmaceuticals, is expected to reach 3.000M CAD sales in less than 4 years from its commercial availability.

Our vision for the company's future earnings is in line with the company's product development. Each new treatment is directed at a bigger market, resulting in a snowball sales effect.

Cumulative revenues for the next 10 years per treatment (in M CAD)



Source: GBC AG

In addition, to generating important revenues for the next 10 years, our model suggests a cumulative long-term net margin of over 85% for all product lines.

Our valuation of the company, as stated previously, is based on our DCF model to which we apply a discount relative to the probability of success for each treatment. Each unique success rate is based on the leading characteristic of each treatment.

Probability of success of each treatment

	Covid-19	Acute Myocarditis	Diastolic Heart Failure
Leading characteristic	FastTrack	Rare Disease	Biosimilar
Phase I-II	*100%	**100%	80%
Phase II-III	*100%	44,6%	50%
Phase III-Approval	73%	60,4%	86,4%
Approval-Commercial	100%	93,6%	93,2%
Combined Success Rate	**73%**	**25,21%**	**32,21%**

**not needed, started with Phase II-III; **already completed*
Sources: Pharma Intelligence[50], GBC AG

[50] Clinical Development Success Rates and Contributing Factors 2011–2020, © BIO | QLS Advisors | Informa UK Ltd 2021

Based on the weighted average of the future revenues for each, we adjusted our DCF model estimate of 49,01 CAD with a resulting success rate of 32,18%, resulting in a target price of 15,77 CAD.

Research has shown that Inflammatory Heart Disease is conducive to responding positively to a Cannabidiol treatment, now it is up to Cardiol Therapeutics to prove it.

Rating: BUY
Target price: 15,77 CAD

DCF MODELL – CARDIOL THERAPEUTICS INC.

Cardiol Therapeutics - Discounted Cashflow (DCF) Betrachtung

Value driver of the DCF model after the estimate phase:

consistency - Phase	
Sales growth rate	95,0%
EBITDA-Margin	85,0%
Depreciation to fixed assets	8,4%
Working Capital to Sales ratio	5,0%

final - Phase	
Eternal growth rate	2,5%
Eternal EBITDA-Margin	85,0%
Eternal effective tax rate	15,0%

Three phases - Model:

Phase	estimate		consistency						terminal
in m CAD	GJ 21e	GJ 22e	GJ 23e	GJ 14e	GJ 25e	GJ 26e	GJ 27e	GJ 28e	value
Sales	0,00	13,40	26,90	6,23	11,22	45,10	229,30	590,90	
Sales changes			100,7%	-76,9%	80,3%	301,8%	408,4%	157,7%	2,0%
Sales to fixed assets	0,00	7,32	10,31	1,84	2,74	9,48	42,81	100,07	
EBITDA	-20,46	-18,35	-1,81	3,11	6,73	31,57	194,91	502,27	
EBITDA-Margin		-136,9%	-6,7%	50,0%	60,0%	70,0%	85,0%	85,0%	
EBITA	-20,69	-18,73	-2,03	2,89	6,45	31,22	194,50	501,81	
EBITA-Margin		-139,8%	-7,5%	46,5%	57,5%	69,2%	84,8%	84,9%	85,0%
Taxes on EBITA	0,00	0,00	0,30	-0,43	-0,97	-4,68	-29,18	-75,27	
Taxes to EBITA	0,0%	0,0%	15,0%	15,0%	15,0%	15,0%	15,0%	15,0%	15,0%
EBI (NOPLAT)	-20,69	-18,73	-1,72	2,46	5,48	26,54	165,33	426,54	
Return on capital	3183,1%	-846,0%	-51,8%	19,5%	118,3%	418,1%	1200,0%	832,8%	350,9%
Working Capital (WC)	1,00	1,50	10,00	1,25	2,24	9,02	45,86	118,18	
WC to Sales		11,2%	37,2%	20,0%	20,0%	20,0%	20,0%	20,0%	
Investment in WC	-2,59	-0,50	-8,50	8,75	-1,00	-6,78	-36,84	-72,32	
Operating fixed assets (OAV)	1,21	1,83	2,61	3,39	4,10	4,76	5,36	5,90	
Depreciation on OAV	-0,23	-0,39	-0,22	-0,22	-0,29	-0,35	-0,40	-0,45	
Depreciation to OAV	18,9%	21,0%	8,4%	8,4%	8,4%	8,4%	8,4%	8,4%	
Investment in OAV	-0,50	-1,00	-1,00	-1,00	-1,00	-1,00	-1,00	-1,00	
Capital employed	2,21	3,33	12,61	4,63	6,35	13,78	51,22	124,08	
EBITDA	-20,46	-18,35	-1,81	3,11	6,73	31,57	194,91	502,27	
Taxes on EBITA	0,00	0,00	0,30	-0,43	-0,97	-4,68	-29,18	-75,27	
Total investment	-3,09	-1,50	-9,50	7,75	-2,00	-7,78	-37,84	-73,32	
Investment in OAV	-0,50	-1,00	-1,00	-1,00	-1,00	-1,00	-1,00	-1,00	
Investment in WC	-2,59	-0,50	-8,50	8,75	-1,00	-6,78	-36,84	-72,32	
Investment in Goodwill	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	
Free cash flows	-23,55	-19,85	-11,00	10,43	3,77	19,11	127,89	353,67	4888,51

Value operating business (due date)	2611,42	2914,79
Net present value explicit free cash flows	235,51	280,92
Net present value of terminal value	2375,91	2633,87
Net debt	8,75	28,13
Value of equity	2602,67	2886,67
Minority interests	0,00	0,00
Value of share capital	2602,67	2886,67
Outstanding shares in m (fully diluted)	53,10	53,10
Fair value per share in CAD	49,01	54,36
Fair value per share with probability of success rate	**15,77**	17,49

Cost of Capital:

Risk free rate	0,3%
Market risk premium	5,5%
Beta	1,93
Cost of Equity	10,9%
Target weight	100,0%
Cost of Debt	10,0%
Target weight	0,0%
Tax-shield	25,0%
WACC	**10,9%**

Return on capital	WACC				
	9,9%	10,4%	10,9%	11,4%	11,9%
349,9%	18,62	17,08	15,73	14,54	13,49
350,4%	18,64	17,10	15,75	14,56	13,51
350,9%	18,67	17,12	**15,77**	14,58	13,52
351,4%	18,69	17,15	15,79	14,60	13,54
351,9%	18,72	17,17	15,81	14,62	13,56

	Covid-19	Acute Myocarditis	Diastolic Heart Failure
Leading characteristic	FastTrack	Rare Disease	Biosimilar
Phase I-II	*100%	**100%	80%
Phase II-III	*100%	44,60%	50%
Phase III-Approval	73%	60,40%	86,40%
Approval-Commercial	100%	93,60%	93,20%
Combined Success Rate	**73%**	**25,21%**	**32,21%**

***** *not needed, started with Phase II-III; **already completed*

ANNEX

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2. The research report is simultaneously made available to all interested investment services companies.

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BUY	The expected return, based on the derived target price, incl. dividend payments within the relevant time horizon is >= + 10%.
HOLD	The expected return, based on the derived target price, incl. dividend payments within the relevant time horizon is > - 10% and < + 10%.
SELL	The expected return, based on the calculated target price, incl. dividend payments within the relevant time horizon, is <= - 10%.

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