Cardiol Therapeutics Inc.

Canada, USA, Germany / Biotechnology
Nasdaq, US; TSX, Canada; FSE, Germany
Bloomberg: CRDL US
ISIN: CA14161Y2006

Initiation of coverage

RATING	**BUY**
PRICE TARGET	**USD 3.60**
Return Potential	601.6%
Risk Rating	High

CARDIOLRX™ – A CANNABIDIOL DRUG WITH BLOCKBUSTER POTENTIAL

Cardiol Therapeutics Inc (Cardiol) is a biotech company with a clinical-stage product pipeline focusing on cardiac diseases triggered by inflammatory processes. The lead oral drug candidate is CardiolRx™, a pharmaceutically manufactured formulation whose active ingredient is cannabidiol. Cannabidiol has shown powerful anti-inflammatory, anti-fibrotic and cardioprotective properties in multiple preclinical studies. CardiolRx™'s lead indication is recurrent pericarditis (RP - inflammation of the sac protecting the heart) for which the company is conducting a phase II open-label pilot US study in 25 patients. The company anticipates headline efficacy results in early 2024 which represent a key milestone for Cardiol. CardiolRx™ is currently undergoing an international phase II study in 100 patients for a second indication, acute myocarditis (AM – heart muscle inflammation). We anticipate efficacy results in H2 2024. Both indications, RP and AM, would qualify CardiolRx™ for orphan drug designation in the US and EU, giving CardiolRx™ 7 years of market exclusivity upon approval. There is no approved first-line therapy for RP or AM and the performance of current standard of care, particularly in life-threatened high-risk patients, is poor. CardiolRx™ has the potential to become the new standard of treatment in RP and AM. We conservatively estimate that if approved, CardiolRx™ could achieve sales of >USD 470m in RP in the US and >USD 970m in AM in the US/EU. We expect positive phase II data from CardiolRx™ in RP to add substantial value to the company and trigger a strong share price appreciation. We initiate coverage of Cardiol with a Buy rating and a USD 3.60 (€3.30) price target.

CardiolRx™ could reach the US market by H2 2026 – Cardiol is pursuing the same fast registration pathway taken by rilonacept (Arcalyst®) The Chairman of CardiolRx™'s phase II study is Dr Allan Klein (Cleveland Clinic), who during the three years to 2021 was the lead investigator who successfully shepherded Kiniksa Pharmaceuticals' rilonacept through phase II and III trials within ~3 years – a record pace for a successful FDA approval as third-line therapy in RP. Cardiol is pursuing this fast and proven registration pathway to maximise success chances and lower development/registration risks. (p.t.o.)

FINANCIAL HISTORY & PROJECTIONS

	2020	2021	2022	2023E	2024E	2025E
Revenue (CAD m)	0.00	0.08	0.00	0.00	0.00	0.00
Y-o-y growth	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
EBIT (CAD m)	-20.69	-38.66	-41.34	-27.00	-24.00	-19.00
EBIT margin	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Net income (CAD m)	-20.64	-31.64	-30.93	-26.50	-23.70	-18.90
EPS (diluted) (CAD)	-0.69	-0.73	-0.49	-0.41	-0.34	-0.26
DPS (CAD)	0.00	0.00	0.00	0.00	0.00	0.00
FCF (CAD m)	-9.17	-23.55	-27.30	-19.68	-19.73	-15.37
Net gearing	-105.7%	-110.0%	-113.9%	-121.7%	-143.6%	-162.4%
Liquid assets (CAD m)	14.03	83.90	59.47	39.74	19.95	14.52

RISKS

Risks include, but are not limited to development, regulatory, competition and financial risks.

COMPANY PROFILE

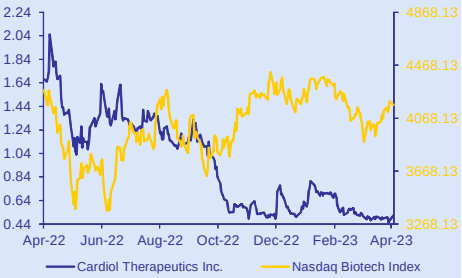
Founded in 2017, Cardiol Therapeutics Inc is a Canadian biotech company focused on the research and development of new drugs to treat heart diseases. The lead drug candidate, CardiolRx™ (cannabidiol) oral solution, is undergoing a US phase II mutli-centre open-label pilot study in 25 patients with recurrent pericarditis and a multi-national phase II study in 100 patients with acute myocarditis.

MARKET DATA

As of 4/10/2023	
Closing Price	USD 0.51
Shares outstanding	64.10m
Market Capitalisation	USD 32.89m
52-week Range	USD 0.45 / 2.05
Avg. Volume (12 Months)	192,090

Multiples	2022	2023E	2024E
P/E	n.a.	n.a.	n.a.
EV/Sales	n.a.	n.a.	n.a.
EV/EBIT	n.a.	n.a.	n.a.
Div. Yield	0.0%	0.0%	0.0%

STOCK OVERVIEW



COMPANY DATA

As of 31 Dec 2022	
Liquid Assets	CAD 59.47m
Current Assets	CAD 61.44m
Intangible Assets	CAD 0.29m
Total Assets	CAD 62.03m
Current Liabilities	CAD 9.80m
Shareholders' Equity	CAD 52.20m

SHAREHOLDERS

MMCAP International Inc	5.2%
Management and Directors	4.4%
Advisorshares Investments LLC	1.7%
Mirae Asset Global Investments Co Ltd	1.7%
Freefloat & others	86.9%

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INVESTMENT CASE

CardiolRx™ – a cannabinoid drug candidate with therapeutic potential in cardiac diseases CardiolRx™ (cannabidiol) is a pharmaceutically manufactured oral solution formulation that is being clinically developed for use in select cardiac diseases in which inflammatory processes contribute to their development and progression. Cannabidiol is emerging as an exciting compound for pharmaceutical applications. In multiple cardiac disease preclinical studies cannabidiol has demonstrated powerful anti-inflammatory, anti-fibrotic and cardioprotective properties. Evidence suggests cannabidiol's mode of action is based on attenuating multiple inflammatory pathways, including inhibiting activation of the well-studied NLRP3 inflammasome. The clinical value of cannabidiol in humans has been validated through the orphan drug Epidiolex®, which was the first cannabidiol compound approved as a therapeutic treatment in rare forms of epilepsy (US approval: 2018). CardiolRx™ is in clinical development in two core cardiac indications, recurrent pericarditis (RP) and acute myocarditis (AM). We believe CardiolRx™ would qualify for orphan drug designation in these two indications and will thus enjoy seven years of market exclusivity in the United States (US) and European Union (EU). Cardiol is also developing a promising subcutaneous formulation of cannabidiol targeting the inflammation and fibrosis typically associated with diastolic heart failure. We anticipate the company may still need about 2 years to prepare a final formulation ready to enter clinical trials in humans.

There is no approved therapy for first-line RP treatment – we estimate CardiolRx™ could generate RP revenue >USD 470m in the US CardiolRx™'s lead indication is RP, a complex inflammatory disorder of the pericardium (sac protecting the heart) that often causes debilitating chest pain, physical limitations, hospitalisation, decreased quality of life, heart failure or even death. RP affects ~40k people in the US. There is no first-line therapy approved for RP and the administered standard treatment with NSAIDs, colchicine and corticosteroids has limitations. In December 2022, a pilot open-label phase II study of CardiolRx™ was initiated in 25 RP patients in the US and results are expected in early 2024. Given the record speed of rilonacept's (Arcalyst®) registration pathway (~3 years), we project CardiolRx™ could reach the market within ~4 years by H2 2026. We have estimated US sales potential in the RP indication of USD 474m five years after launch. Our estimate is conservative, considering that Epidiolex® achieved impressive revenue of USD 736.4m (+12%) in 2022, its fourth year after market launch, in an indication with a lower incidence of 37k patients p.a. The only approved RP therapy, rilonacept (Arcalyst®), is primarily used as a third-line intervention and achieved USD 122.5m revenue in 2022, i.e. during 12 months beginning almost a year after launch, targeting the ~14k RP patients with ≥2 recurrences.

AM lacks an approved treatment – we project >USD 970m AM revenue potential for CardiolRx™ in the US and EU Myocarditis is an uncommon, potentially life-threatening inflammatory disease of the heart muscle (myocardium), caused predominantly by viral infection. Based on an estimate of 16.2 AM cases per 100k persons p.a. (Wang *et al*., 2021), there are ~54k AM patients p.a. in the US and ~72k p.a. in the EU. In August 2022, Cardiol started the international phase II ARCHER study with 100 patients at major cardiac centres in North America, Europe, Latin America, and Israel. We expect to see efficacy results by H2 2024 which will act as the basis for licensing with a pharmaceutical partner who would fund and conduct a pivotal phase III study. We expect a potential drug approval and market launch in the US and EU in H2 2028. We project Cardiol to achieve peak sales by 2033 of USD 652m in the US and USD 323m in the EU.

Pericarditis and myocarditis treatment markets to show a healthy growth dynamic in the period 2022-2032 The global pericarditis drugs market was valued at USD 3.6bn in 2022, and is expected to reach USD 6.0bn by 2032, expanding at a CAGR of 5.2% over this period. Also, the global myocarditis market is an attractive niche worth approx. USD 1.6bn in 2021 growing by a CAGR of 6.2% to achieve USD 2.6bn by 2029 (sources: Bridge Market Research, 2022; Future Market Insights, 2022).

Cardiol shares appear significantly undervalued. We initiate coverage with a price target of USD 3.60 (€3.30) and a Buy recommendation Based on the assessment of CardiolRx™ in the two leading indications, RP and AM, our proprietary risk-adjusted sum-of-the-parts valuation model suggests a fair value for Cardiol of USD 3.60 p/s (€3.30 p/s). The company is well funded to implement the business model. Based on a sound cash position of CAD 59.5m (USD 43.9m) at YE 2022, management guides that the cash runway extends into 2026. The reported net cash position equated to ~CAD 0.93 p/s or USD 0.68 p/s. The current share price of USD 0.51 p/s represents a discount of ~25% to net cash which in our view is unwarranted. We suspect sentiment is still affected by the cancellation in October 2022 of the phase II/III LANCER study for the COVID-19 inflammation indication. However, we expect that positive newsflow on CardiolRx™'s RP phase II study will enable investors to recognise the value of Cardiol's pipeline, improving sentiment and triggering strong share price appreciation.

SWOT ANALYSIS

STRENGTHS

- **Experienced management team** David Elsley (President and CEO), Chris Waddick (CFO), Dr Andrew Hamer (CMO and Head of R&D) and Bernard Lim (COO) are highly qualified and seasoned executives with over 120 years of combined experience in the pharmaceutical and life science (in particular the cardiology field) industries.

- **Unique lead cannabinoid-based drug candidate with well-studied anti-inflammatory NLRP3-modulating mode of action** CardiolRx™'s cannabinoid active pharmaceutical ingredient (API) has proved its powerful anti-inflammatory, anti-fibrotic and cardioprotective properties in multiple cardiac disease preclinical studies. Data suggests cannabidiol's mode of action in heart diseases is based on attenuating multiple inflammatory pathways, including inhibiting activation of the NLP3 inflammasome. The clinical value of cannabidiol in humans has been validated through the cannabidiol-based drug Epidiolex®, the first drug approved for the treatment of rare forms of epilepsy.

- **Deep expertise and network in the company's core cardiology field** To enhance its cardiology expertise, Cardiol has appointed three leading experts in the cardiology field to its Scientific Advisory Board. It has also established a powerful key opinion leader team of 16 investigators from top cardiac centres to support the clinical trials, including Dr Allan Klein (Cleveland Clinic), Dr Dennis McNamara (University of Pittsburgh) and Dr Leslie Cooper (Mayo Clinic), as well as an R&D collaboration with international academic centres of excellence, including the Houston Methodist DeBakey Heart & Vascular Center (US), TecSalud del Tecnológico de Monterrey (Mexico), and the University of Alberta (Canada).

- **Cash runway into 2026** Based on a sound cash position of CAD 59.5m at YE 2022, management guided that with these funds the company can finance operations into 2026.

WEAKNESSES

- **Early stage pipeline, with three programmes based on the same active ingredient** The lead drug candidate, oral CardiolRx™ for the two cardiac diseases recurrent pericarditis and acute myocarditis, has recently started phase II development in both indications. The third indication for the same active ingredient with a subcutaneous formulation is still in the preclinical stage. Despite Cardiol's and academia's strong preclinical efficacy data on the compound, efficacy and response rate have yet to be demonstrated in patients with these conditions.

- **Lack of technology platform** The company does not own a technology platform which would allow it to generate further drug candidates in the future. For this purpose, the company is highly dependant on its cannabidiol formulation expertise and potential technologies from its network of collaborators.

OPPORTUNITIES

- **CardiolRx™'s progress in phase II clinical trials in recurrent pericarditis may create significant shareholder value** This pilot clinical trial with 25 patients will provide highly valuable efficacy data within <12 months paving the way for a phase III registration study.

- **Additional value upside from other pipeline cannabidiol formulations** Cardiol is currently focusing its resources on CardiolRx™'s lead indications, recurrent pericarditis and acute myocarditis. The company has a further attractive heart failure preclinical programme based on a subcutaneously administered cannabidiol formulation with substantial value-generation potential. Preclinical *in vitro* data for the drug candidate in a cardiac failure model has provided promising results. We believe this programme may need about two years to enter the clinic.

- **Development deals with pharmaceutical companies** The company aims to close a collaboration agreement with a pharmaceutical company for the expensive phase III development of CardiolRx™ in the AM indication. A deal of this type would in our view validate the drug's potential and attract attention from the industry for further potential co-development deals. We believe management would consider licensing certain less valuable non-core Asian or middle-East territories to access an additional, non-dilutive source of funding.

THREATS

- **Development and regulatory risks** Development of the lead drug candidate CardiolRx™ may progress slower than expected. The product may also fail to demonstrate efficacy in both ongoing phase II trials in recurrent pericarditis and acute myocarditis, or in the pivotal phase III trials (even though the preclinical investigation has shown excellent anti-inflammatory and anti-fibrotic effects of the cannabidiol-based molecule in these types of cardiac diseases). The preclinical development of CardiolRx™'s subcutaneous formulation may also fail to achieve the desired performance, given that it is challenging to reformulate cannabidiol, a naturally occurring oil molecule, into a compound with aqueous behaviour (i.e. water solubility). Moreover, even if CardiolRx™ achieves good results in clinical trials, there is still a risk that the regulatory agencies (FDA and EMA) will not approve the drug or may request further trials.

- **Competitive risks** Cardiol's pipeline, particularly the lead drug candidate CardiolRx™, may face competitive pressure. Several pharmaceutical and biotech companies, including TRPHARM (phase II-III), Cantargia (late-preclinical), Inflamma Therapeutics (mid-preclinical) and Evotec (early-preclinical) are developing new therapies for treating recurrent pericarditis or acute myocarditis. Any unexpected breakthrough by one or more competitors could hit Cardiol's potential revenues.

- **Financing risks** While the company is funded through 2026, it will still need to raise funds by 2025 to finance further development of its R&D portfolio until profitability is reached after 2026. Delays or negative results from clinical trials or a difficult financing environment could impede the raising of additional capital.

VALUATION

Biotechnology valuation is notoriously difficult since there is a high risk in developing the R&D pipeline, which leads to uncertainty in projecting cash flows. We have assessed Cardiol Theraputics' fair value based on a sum-of-the-parts methodology (SOTP). We believe this is the most appropriate valuation method for the company because it reflects the implicit risk-adjusted value of every drug candidate in the R&D pipeline. Development risks, including clinical and regulatory risks, are considered, as are market size and the expected timing of cash flows post-approval for each project.

We have used a risk-adjusted NPV model for the lead drug candidate CardiolRx™ in the two key development-stage indications, recurrent pericarditis (RP) and acute myocarditis (AM). We believe that CardiolRx™ also has value in the heart failure indication. However, this indication is still in the preclinical stage (up to 2 years away from entering the clinic) embedding significant development risk, we thus regard it as upside to our valuation.

During the forecasting process, we adjusted our sales projections and resulting cash flows for estimated success probabilities to obtain risk-adjusted expected values. We base our probability coefficients on statistical sector studies, such as DiMasi *et al.*, and on our own estimates. In this instance, we have derived a 48% probability of success in the RP indication (phase II, clear development pathway following rilonacept's (Arcalyst®) approval - see details on page 26) and a 38% success probability in the AM indication (phase II, development pathway to be established).

Additionally, using First Berlin methodology, which takes company-specific risk factors into account, we have derived a cost of equity (COE) of 17.0% for Cardiol Theraputics. Based on a debt ratio of 0.0%, we arrive at a WACC estimate of 17.0%, which we have used to discount projected cash flows. Including projected proforma net cash of USD 57.9m (CAD 78.5m), we value Cardiol Therapeutics at USD 288.5m, which implies a fair value of USD 3.60 (€3.30) per share on a proforma fully diluted basis. At the moment we consider the RP indication to be the most important value driver for the company. Our SOTP model shows that CardiolRx™'s RP indication accounts for around 60% of the pipeline value. Using our ten-factor risk analysis, we have set a High-risk rating for Cardiol Therapeutics. The main risk factors that we have identified are development, regulatory, competition and financing.

Table 1: "Sum-of-the-parts" valuation model

Compound	Project[1]	Present Value	Patient Pop (K)	Treatment Cost (USD)	Market Size (USDM)	Market Share (%)	Peak Sales (USDM)	PACME Margin[2] (%)	Discount Factor (%)	Market Exclusivity[3] (years)	Time to Market (years)
CardiolRx™	RP - US	USD 171.2M	40K	52,000	2,080.0M	18%	474.3M	30%	17.0%	7	4
CardiolRx™	AM - US	USD 89.2M	54K	52,000	2,808.0M	18%	652.1M	20%	17.0%	7	6
CardiolRx™	AM - EU	USD 34.0M	72K	18,000	1,296.0M	18%	322.9M	20%	17.0%	7	6
PACME PV		USD 294.4M			6,184.0M		1,449.3M				
Costs PV[4]		USD 63.8M									
NPV		USD 230.6M									
Milestones PV		USD 0.0M									
Net cash (proforma)		USD 57.9M									
Fair Value		USD 288.5M									
Share Count (proforma)		79,186K									
Price Target		USD 3.60									
Price Target		EUR 3.30	(based on EUR-USD exchange rate of 1.09)								

1) A project typically refers to a specific indication or, where necessary or relevant, a combination between indication and geographic market

2) PACME (Profit After Costs and Marketing Expenses) reflects the company's profit share on future revenues. This share may be derived in the form of royalties (outsourced marketing/manufacturing) or operating EBITDA margin (in-house model), or some mix of both (depending on the specific parameters of partnership agreements)

3) Remaining market exclusivity after the point of approval

4) Includes company-level R&D, G&A, Financing Costs and CapEx; COGS and S&M are factored into the PACME margin for each project

Source: First Berlin Equity Research

Assessment of our SOTP valuation

We estimate Cardiol is worth USD 289m. We believe this value is quite conservative since we have seen comparable companies with drug candidates of similar potential in phase II trials worth much more than this figure. We have identified two biotech peers worth taking a closer look at and describe these cases below to better understand Cardiol's substantial value. These are GW Pharma and MyoKardia.

- **GW Pharmaceuticals Plc (GW)** was a British biopharmaceutical company developing and commercialising novel therapeutics from its proprietary plant-derived cannabidiol product platform. The company pioneered the development of cannabis drugs for orphan drug indications, including Sativex®, a THC-based drug approved for multiple sclerosis spasticity in 2010 and Epidiolex®, a liquid formulation of cannabidiol approved in 2018 to treat severe forms of epilepsy (Lennox-Gastaut syndrome and Dravet syndrome). In 2001, at the time of its IPO on the AIM in the UK, its pipeline was in phase II development. The company was then valued at a market cap in the USD 100m range and occasionally even below this level until about 2013. In May 2013, the company was listed on the US Nasdaq, and by year-end, its market cap had jumped to ~USD 610m. A year later, the market cap had doubled, and in 2017-2018 following Epidiolex®'s positive results and US approval, the market cap increased to the USD 3.0-3.8bn level. In 2021 the company was acquired by Jazz Pharmaceuticals for USD 7.2 bn. Epidiolex® was launched in November 2018, achieving revenue of USD 510m in 2020, USD 658m (+29%) in 2021 and USD 736.4m (+12%) in 2022, its fourth year after launch. Epidiolex® is the first cannabidiol drug approved ever, validating cannabidiol in therapeutic use.
- **MyoKardia Inc** was a US-based biomedical company founded in 2013, developing small molecule drugs for patients with genetic heart diseases such as hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy. Cardiomyopathy is an orphan drug indication affecting about 30k young people in the US. HCM affects 160-200k people in the US. Myokardia's market cap was ~USD 400m in 2015-2016, when its pipeline was at a similar development stage to Cardiol Therapeutics today. Following the publication of MyoKardia's Phase II trial results of mavacamten (Camzyos®) in HCM in 2017, the company's valuation rose to over USD 1.5bn. Positive results in a second phase II study of mavacamten in HCM in 2019 drove a further market cap expansion to USD 3.4bn by year-end. The company was acquired by Bristol Myers for USD 13.1bn in cash in 2020.

Cardiol's market cap is currently below its cash position As of YE 2022, the reported net cash position of Cardiol was CAD 59.5m or USD 43.9m, which divided by the reported 64.1m shares outstanding equates to CAD ~0.93 p/s or USD 0.68 p/s. Surprisingly, Cardiol is trading at a market cap of USD 33m or USD 0.51 p/s, representing a discount of ~25% to net cash. These numbers give the pipeline a value below zero which is, in our view, unwarranted.

PRODUCTS – DETAILED ANALYSIS

Estimation of price, sales potential and product value

Oral CardiolRx™ in RP patients in the US Recurrent pericarditis is a complex inflammatory disorder and often causes debilitating chest pain, physical limitations, hospitalisation, decreased quality of life, heart failure or even death. In December 2022, a pilot phase II study of the compound was initiated in the US. Based on statistics provided by the American Heart Association, ~125k patients p.a. suffer from acute pericarditis in the US and ~30% of them, or ~40k people, are affected by recurrent pericarditis. No first-line therapy is approved for RP, and the administered standard treatment with NSAIDs, colchicine, and corticosteroids is unsatisfactory. The drug rilonacept (Arcalyst®) is approved

and used as a third-line therapy of RP (see RP disease chapter). In our view, CardiolRx™ could capture a substantial portion of this target population upon approval as first-line therapy.

We have conservatively assumed a list price per treatment course per year of USD 70k coupled with ~25-30% discounts to insurance providers, equating to an average ex-factory therapy price of USD 52k p.a. We note that the comparable RP biologic drug rilonacept (Arcalyst®) has a list price >USD 200k for a 12-month course, which may equate to >USD 150k after discounts. Our assumed CardiolRx™'s price is very conservative compared to rilonacept (Arcalyst®). However, we note that rilonacept is a biologic drug and therefore, expensive to produce. Our estimated price would promote the achievement of faster reimbursement and market penetration by CardiolRx™.

We have assumed that this segment will grow at a CAGR of 3% by 2040. We expect CardiolRx™ to achieve a penetration rate of 18%, leading to peak sales of USD 474m five years after market launch. We believe this estimate is very conservative. The cannabidiol-based epilepsy drug Epidiolex® achieved peak sales of USD 736.4m (+12%) in its fourth year after launch in an indication with a lower incidence of 37k patients p.a. Rilonacept (Arcalyst®) achieved revenue of USD 122.5m in 2022, i.e. during 12 months beginning almost a year after launch, targeting ~14k RP patients with ≥2 recurrences. We believe CardiolRx™ qualifies well for orphan drug designation and will thus enjoy seven years of market exclusivity in the US. Cardiol also has solid patents on the drug's use and formulation suggesting further years of protection before potential generics can receive approval. We project a potential US approval and market launch in H2 2026.

Table 2: Assumptions of CardiolRx™ in RP patients in the US (currency: USD)

CardiolRx™ RP - US	Present Value	Patient Pop	Treatment Cost	Market Size	Market CAGR	Market Share	Peak Sales	PACME Margin	Discount Factor	Market Exclusivity
Parameters	$171M	40K	$52,000	$2,080M	3%	18%	$474M	30%	17.0%	7

Source: First Berlin Equity Research (estimates currency: USD)

Considering the potentially small size and cost of a registration phase III study, we have assumed that Cardiol will conduct it on its own to maximise profitability and value generation. We thus assume that Cardiol will out-license the drug following successful phase III trials to a pharmaceutical partner, leading to an attractive PACME royalty rate of 30% of sales. The partner will conduct commercialisation and bear the marketing expenses. Cardiol's royalties will roughly equate to its profit on the product. These assumptions are in accordance with metrics we have observed in the industry.

Potential development of CardiolRx™ in RP in the EU represents upside to our valuation For the time being, we assume Cardiol will focus its development strategy on the highly lucrative US market and do not include the EU in our financial model, providing potential future upside.

CardiolRx™ in AM patients in the US and the EU Similarly to RP, CardiolRx™ has shown promise in treating AM. Myocarditis is an uncommon, potentially life-threatening inflammatory disease of the heart muscle (myocardium) caused predominantly by virus infection. The disease leads to dilated cardiomyopathy (DCM – it is a leading cause of cardiac transplantation) in up to 30% of cases, acute and fulminant heart failure or even sudden cardiac death. Based on an estimate of 16.2 cases per 100k persons p.a. (Wang *et al.*, 2021), ~54k people suffer from AM in the US and ~72k p.a. in the EU. Based on this incidence, the drug meets the requirements for orphan drug designation in our view. There is currently no approved therapy for AM (see AM disease chapter), and we see potential substantial demand if the drug is approved. In August 2022, Cardiol started an international phase II ARCHER study with 100 patients at major cardiac centres in North America, Europe, Latin America, and Israel. We expect that Cardiol will initially focus on the

two main regions of US/Canada and Europe. In the US, we estimate an average ex-factory therapy price of USD 52k for a one-year treatment similar to the RP indication. In Europe, where prices are typically substantially below the US level, we assumed an average ex-factory therapy price of USD 18k.

We assume that the company will license the product to a pharmaceutical partner after the successful completion of the ongoing phase II study, receiving a royalty rate of 20% upon commercialisation. We assume the US/European partner will fund the phase III development expenses. Given that the drug candidate has recently initiated phase II, we project a potential approval and market launch in H2 2028. Based on an anticipated penetration rate of 18% in both regions, we conservatively expect Cardiol to achieve peak sales by 2033 of USD 652m in the US and USD 323m in the EU.

Table 3: Assumptions for CardiolRx™ in AM patients in the US and the EU (currency: USD)

CardiolRx™ AM - US	Present Value	Patient Pop	Treatment Cost	Market Size	Market CAGR	Market Share	Peak Sales	PACME Margin	Discount Factor	Market Exclusivity
Parameters	$89M	54K	$52,000	$2,808M	3%	18%	$652M	20%	17.0%	7
CardiolRx™ AM - EU	Present Value	Patient Pop	Treatment Cost	Market Size	Market CAGR	Market Share	Peak Sales	PACME Margin	Discount Factor	Market Exclusivity
Parameters	$34M	72K	$18,000	$1,296M	3%	18%	$323M	20%	17.0%	7

Source: First Berlin Equity Research (estimates currency: USD)

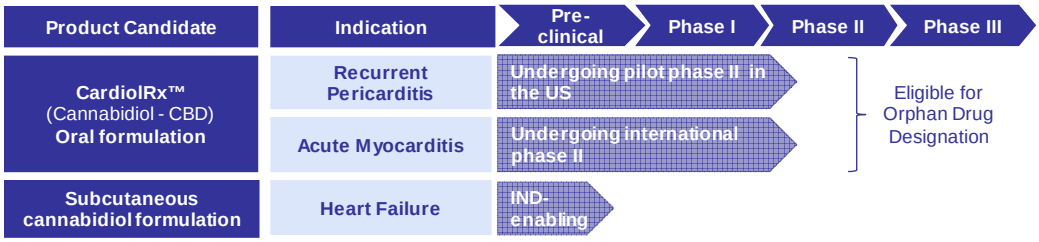
COMPANY PROFILE

OVERVIEW

Cardiol Therapeutics Inc Founded in 2017 and headquartered just outside of Toronto in Oakville, Ontario, Canada, Cardiol Therapeutics Inc (Cardiol) is a clinical-stage biotech company focused on researching and developing innovative drugs for cardiac diseases with unmet medical need. The company was founded by David Elsley (President and CEO), Dr Eldon Smith and Dr Anthony Bolton based on their >25-year inflammation and cardiology expertise and new insights from their extensive review of scientific literature searching for new approaches in the field. The scientific basis of the company was established in December 2010. The publication in the *Journal of American College of* Cardiology titled "Cannabidiol Attenuates Cardiac Dysfunction, Oxidative Stress, Fibrosis, and Inflammatory and Cell Death Signaling Pathways in Diabetic Cardiomyopathy" (Mohanraj Rajesh *et al.*, 2010) described cannabidiol as a promising molecule in heart failure pathology due to its anti-inflammatory, anti-fibrotic and cardioprotective properties.

Clinical-stage portfolio – it can benefit from 7-year market exclusivity protection through orphan drug designation The active pharmaceutical ingredient in Cardiol's current portfolio of products is pharmaceutically manufactured cannabidiol. The company has formulated its lead oral drug candidate CardiolRx™, which is in clinical development in two cardiac indications, recurrent pericarditis and acute myocarditis. Both indications qualify CardiolRx™ for orphan drug designation, which is usually granted by the US and European regulatory agencies FDA and EMA for rare diseases that affect <200k people in the respective jurisdictions. Orphan drugs receive certain incentives such as 7-year marketing exclusivity, tax credits, expedited review and waiver of registration fees. The company also has a subcutaneous cannabidiol formulation in preclinical development for heart failure. We give an overview of the R&D pipeline in figure 1 below.

Figure 1: Snapshot of the R&D pipeline focusing on cardiac diseases



Source: First Berlin Equity Research, Cardiol Therapeutics Inc

Sound IP portfolio…The company's world-class scientific team formulated the lead oral compound CardiolRx™ (active substance cannabidiol) and developed substantial intellectual property (IP) used in its innovative formulation capable of efficiently delivering the drug to the inflammation sites in the heart. We have identified five core patents held by Cardiol Therapeutics which protect CardiolRx™'s oral (1 & 2) and subcutaneous (3, 4 & 5) formulations. In addition, the product is protected through its manufacturing partners' IP, such as Noramco's patent (US 2017/0008868 A1) to manufacture its cannabidiol active pharmaceutical ingredient (API).

Table 4: Overview of Cardiol Therapeutics' patent portfolio

Nr	Publication number	Priority date	Publication date	Assignee	Title
1	WO2022120457A1	2020-12-07	2022-06-16	Cardiol Therapeutics	Stable oral cannabidiol compositions
2	WO2021046628A1	2019-09-09	2021-03-18	Cardiol Therapeutics	Stable medicinal cannabidiol compositions
3	WO2022174352A1	2022-02-18	2022-08-25	Cardiol Therapeutics	Injectable cannabinoid formulations
4	WO2021077211A1	*2019-10-25	2021-04-29	Cardiol Therapeutics	Cannabidiol compositions for use in treating heart conditions
5	WO2019113685A1	2017-12-12	2019-06-20	Cardiol Therapeutics	Amphiphilic block copolymers, micelles, and methods for treating or preventing heart failure

Source: Google patent database, First Berlin Equity Research

Lean R&D structure comprising own expertise and complemented by cooperation partners' technologies and know-how Cardiol's founders have implemented a resource-efficient R&D structure that combines their cardiology, inflammation and clinical development expertise with complementary external scientific and technological resources in key areas from well-chosen cooperation partners.

Scientific network The company has appointed to its Scientific Advisory Board three leading experts in the cardiac field: 1) Dr Paul M. Ridker, Director of the Center for Cardiovascular Disease Prevention, a translational research unit at Brigham and Women's Hospital (BWH). He is also Professor of Medicine at Harvard School of Medicine (HMS). 2) Dr Bruce McManus, Professor Emeritus at the Department of Pathology and Laboratory Medicine in the University of British Columbia. He has served as CEO at the Centre of Excellence for Prevention of Organ Failure, Director at the UBC Centre for Heart Lung Innovation and Scientific Director at the Institute of Circulatory and Respiratory Health; 3) Dr Joseph A. Hill, Professor of Internal Medicine and Molecular Biology, Chief of Cardiology at UT Southwestern Medical Center, Dallas, TX and Director of the Harry S. Moss Heart Center. In addition, the company has a team of 16 leading investigators from top cardiac centres supporting the clinical trials (e.g. steering committee), including 1) Dr Allan Klein from the Cleveland Clinic - Chair of the recurrent pericarditis phase II study; 2) Dr Dennis McNamara, Professor of Medicine at the University of Pittsburgh and 3) Dr Leslie Cooper, General cardiologist and Chair of the Mayo Clinic Enterprise Department of Cardiovascular Medicine –they are Chair and Co-Chair of the acute myocarditis phase II study.

R&D network In August 2018, Cardiol Therapeutics established an R&D collaboration focused on developing nanotherapeutics to treat select heart diseases with international academic centres of excellence, including the University of Alberta (Canada), the Houston Methodist DeBakey Heart & Vascular Center (US) and TecSalud del Tecnológico de Monterrey (Mexico), as well as the companies Nano4heart (nanomedicine spin-off from TecSalud) and Meros Polymers Inc (polymertech spin-off from Alberta University). These new technologies are at an early development stage.

Supplier network In June 2017, the company closed an exclusive supply agreement with the pharmaceutical manufacturing specialist Dalton Pharma Services (Dalton) to manufacture the specified CardiolRx™ formulation. Dalton is a Health Canada-approved, US Food and Drug Administration (FDA)-registered and current Good Manufacturing Practice (cGMP) manufacturer of >200 drugs, including pharmaceutical cannabinoids. Its manufacturing capability is scalable to commercial quantities. Cardiol has also secured the required active pharmaceutical ingredients (APIs) in high purity from Noramco Inc (i.e. subsidiary Purisys LLC).

Table 5: Overview of Cardiol's R&D and supplier network

Academic institutions (centres of excellence)	Expertise	Companies	Expertise
University of Alberta	Cardiology/Polymers	Meros Polymers Inc	Polymer drug delivery formulation
TecSalud del Tecnológico de Monterrey	Cardiology/Nanoscience	Nano4heart	Nanotech drug delivery formulation
Houston Methodist DeBakey Heart & Vascular Center	Cardiology	Dalton Pharma Services	Pharmaceutical manufacturing
		Noramco (Purisys)	Cannabinoid API supplier

Source: First Berlin Equity Research, Cardiol Therapeutics Inc

We believe the company will continue to source new promising molecules and technologies supported by its partner network to expand its product pipeline in the future. So far, management has disclosed almost no details on the technologies used to develop its proprietary subcutaneous formulation of CardiolRx™.

DEVELOPMENT STRATEGY

Strategy focused on its CardiolRx™'s drug candidate The company has established a clear development strategy for CardiolRx™ prioritising the three existing indications as follows:

1. The first priority is the conduct and completion of the recently started pilot II clinical study over a period of ~1 year in the lead recurrent pericarditis indication. This product has the fastest route-to-market potential (FBe: ~3.5-4 years).
2. The second priority is the completion of phase II clinical trials over ~2 years in the acute myocarditis indication.
3. The third priority is completing CardiolRx™'s subcutaneous formulation and obtaining the IND for the phase I clinical trial (FBe: ~2 years) in heart failure.

In October 2022, the company halted it's the phase II/III LANCER study it had started in the COVID-19 indication once it saw a strongly decreasing trend in the number of eligible patients and a lower-than-anticipated event rate in the study (i.e. the severity of disease caused by the circulating virus variants declined). In our view, this was the right decision, and the company's cash runway was extended by ~1 year into 2026. With regard to CardiolRx™'s three core indications, we expect the company to out-license CardiolRx™'s commercial rights to pharmaceutical companies once phase II trials are completed. The partners will finance the cost-intensive phase III clinical trials. The company will reduce risk and R&D costs and benefit from the pharmaceutical partners' expertise, financial resources, marketing muscle, and experience. However, given CardiolRx™'s potential quick route-to-market in recurrent pericarditis and the small phase III study size, the most attractive option is to complete this development independently, thereby maximising the drug's value.

DUAL LISTING ON US NASDAQ & CANADIAN TSX, TRADE ON GERMAN EXCHANGES

Listings opened doors for access to new funds – USD 50m raised after US Nasdaq listing in 2021 To finance business development further, Cardiol Therapeutics went public with an IPO. The shares started trading on the Toronto Stock Exchange (TSX) on 20 December 2018. In connection with the IPO, the company placed 3.4m units, including a partial exercise by the underwriters of the Over-Allotment-Option, at a price of CAD 5 p/u, raising gross proceeds of CAD 16.9m. On 30 May 2019, the shares also began trading on the US OTCQX Best Market. In 2020, the company raised net proceeds of CAD 16.3m, including equity placement and warrant conversion. In May 2021, the company conducted a private placement of 6.1m units at CAD 3.60 p/u raising CAD 22.0m. On 10 August 2021, the OTCQX listing was replaced with one on the Nasdaq Capital Market, which should expand its access to investors and increase stock liquidity (trading volume). Shortly afterwards, in November, the company raised further funds amounting to USD 50.2m by placing 16.4m units at a price of USD 3.07 p/u. In 2021, the raised net proceeds totalled CAD 93.5m, including the issued units and conversion of warrants and options. In January 2021, Cardiol also registered the shares for trading in Germany on all main German Stock Exchanges to expand its exposure to European investors.

Potential dilution As of 29 March 2023, the company had 64.1m shares outstanding. While the company is well financed into 2026, there is further potential share dilution totalling 15.7m shares in connection with 11.6m warrants expiring in 2024 (exercise price of CAD 4.60-5.12), 1.2m stock options expiring in the period 2025-2027, 600k performance share units outstanding for certain consultants and 2.3m restricted shares subject to vesting. Cardiol also has in place the "2022 at-the-market offering program" (ATM) with Canaccord and Cantor Fitzgerald, through which the company has the option to sell shares worth a total value of USD 50m.

Is the Nasdaq listing at risk? On 14 November 2022, Cardiol received a Nasdaq notice of non-compliance with the minimum required bid price of USD 1. If not resolved within six months, plus a potential six-month extension, this could lead to delisting. We believe Cardiol is committed to the Nasdaq listing and actively considering various strategies to maintain it.

THE LEAD DRUG CANDIDATE ORAL CARDIOLRX™ SHOWS PROMISE IN CARDIAC DISEASES

PRODUCT PROFILE

CardiolRx™ solution – product description (active pharmaceutical ingredient cannabidiol) CardiolRx™ (cannabidiol) is a pharmaceutically manufactured oral solution formulation that is being clinically developed for use in select cardiac diseases in which inflammatory processes contribute to their development and progression. The product's formulation is manufactured under current good manufacturing practice regulations (cGMP), meeting the highest industry standards related to purity, stability and batch consistency. Oral CardiolRx™ is being studied in two indications. The lead indication is recurrent pericarditis (inflammation of the sac surrounding the heart called the pericardium), in which the company is conducting a phase II open-label pilot study in 25 patients. The second lead indication is acute myocarditis (heart muscle inflammation); it is currently undergoing a phase II study in 100 patients.

Figure 2: CardiolRx™ oral solution

Source: Cardiol Therapeutics Inc

Cannabidiol is a main component of cannabis Cannabidiol is emerging as an exciting compound for pharmaceutical applications. Cannabidiol is one of the major constituents of cannabis, a plant belonging to the Cannabaceae family. There are over a hundred different relevant chemical components (cannabinoids) in the cannabis plant. However, research has focused on two main components: cannabidiol and tetrahydrocannabinol (THC). THC is psychoactive and produces the typical cannabis high. Cannabidiol produces no high and sometimes counteracts the high of the THC. Most attention from scientists is currently placed on cannabidiol, which is considered safe and not likely to cause physical dependence or abuse. This makes cannabidiol particularly attractive for medicinal use.

Cannabidiol has natural formulation limitations, particularly in oral administration Unfortunately, cannabidiol administered orally has two main limitations in pharmaceutical application:

1) Cannabidiol is by nature an oil molecule — it is therefore lipophilic (dissolves in oil), having a poor water solubility of only 0.7µg/mL (source: Pharmaceutical Technology, 2020). Poor solubility is one of the most critical barriers to achieving a desired drug concentration in systemic circulation and the required pharmacological response. Due to its lipophilic characteristic, cannabidiol may dissolve better in the fat content of food, increasing its solubility, absorption and bioavailability when administered orally in a fed state. This has been demonstrated by many similar pharmacological drugs (Winter *et al.*, 2013).

2) Cannabidiol undergoes extensive first-pass metabolism (i.e. biotransformation in the gut, liver and excretion via kidneys). Consequently, this compound cannot readily be absorbed orally and has a low bioavailability of merely 6% (amount of cannabidiol that reaches the systemic circulation), requiring a large quantity to have a medicinal effect.

Cardiol Therapeutics overcame these limitations by using a high-concentration, stable formulation with an extended shelf life of > 2 years Cardiol's formulation utilises high-purity synthetic cannabidiol coupled with a solvent and an antioxidant to ensure a high concentration and stable product. The stability of such a preparation is critical since cannabidiol can dramatically change over time, and toxic or undesired by-products could arise during storage. Cardiol's formulation facilitates high cannabidiol concentration and does not require enhanced aqueous solubility. The antioxidant extends the compound shelf life from 90 days (i.e. botanical extract) to well over two years.

Cardiol's synthetic cannabidiol has several advantages over plant-derived cannabidiol Cardiol Therapeutics has chosen to incorporate synthetic pharmaceutically manufactured cannabidiol into its drugs due to its superior quality and very high purity (e.g. free of THC and heavy metals / fertilisers / pesticides), ease of meeting strict regulations, batch consistency, high yield allowing large-scale production and lower cost. According to a 2019 Nature article, Ginkgo Bioworks/Cronos Group produced synthetic cannabidiol for <USD 1k per kg while high-quality plant-extracted cannabidiol was selling for a wholesale price of >USD 5k/kg. Synthetic cannabidiol is an ultra-pure crystalline powder manufactured via organic chemistry. Synthetic cannabidiol has a relatively simple molecular structure (chemical formula: C21H30O2), facilitating production in regulated pharmaceutical facilities. Regarding cannabidiol's performance depending on its origin, there are no head-to-head clinical studies comparing the efficacy of synthetic versus plant cannabidiol. However, an open-label study assessing the efficacy, safety and pharmacokinetic parameters of synthetic cannabidiol in 35 drug-resistant epilepsy patients found a very similar performance compared to naturally-occurring cannabidiol (source: Klotz *et al*., 2019). Also, an *in-vitro* study demonstrated that there is no pharmacological difference in the anti-inflammatory, antiproliferative or permeability effects of both substances (source: Maguire *et al*., 2021). We thus believe the synthetic compound to be pharmacologically identical to purified cannabidiol. The other advantages, such as high purity, batch consistency, ease of scalability and cost, are the major factors determining the overall superiority of the synthetic compound.

ACADEMIC RESEARCH SUGGESTS STRONG ACTIVITY OF CANNABIDIOL IN MANAGING INFLAMMATION AND HEART DISEASES

Cannabidiol shows promise in the treatment of several diseases, including cardiac disorders Preliminary evidence suggests that cannabinoids, particularly cannabidiol, are effective in several diseases such as cancer (e.g. dronabinol and nabilone are two FDA-approved drugs containing THC that reduce the side effects of chemotherapy), epilepsy (e.g. the FDA-approved drug Epidiolex® is a compound that contains highly purified cannabidiol from the cannabis plant), heart diseases, HIV/AIDS, chronic pain, multiple sclerosis and glaucoma (source: US National Institutes of Health).

Table 6: Overview of currently approved cannabinoids

Name	API	Administration Route / Dosage Form	Disease	Application	Development Stage
Dronabinol	THC	Oral / capsule & solution	HIV, chemotherapy	Anorexia, nausea	Market
Nabilone	THC analogue	Oral / capsule	Chemotherapy, chronic pain	Nausea, pain	Market
Epidiolex	CBD	Oral / solution	Lennox-Gastaut and Dravet syndromes	Epilepsy	Market

Source: First Berlin Equity Research

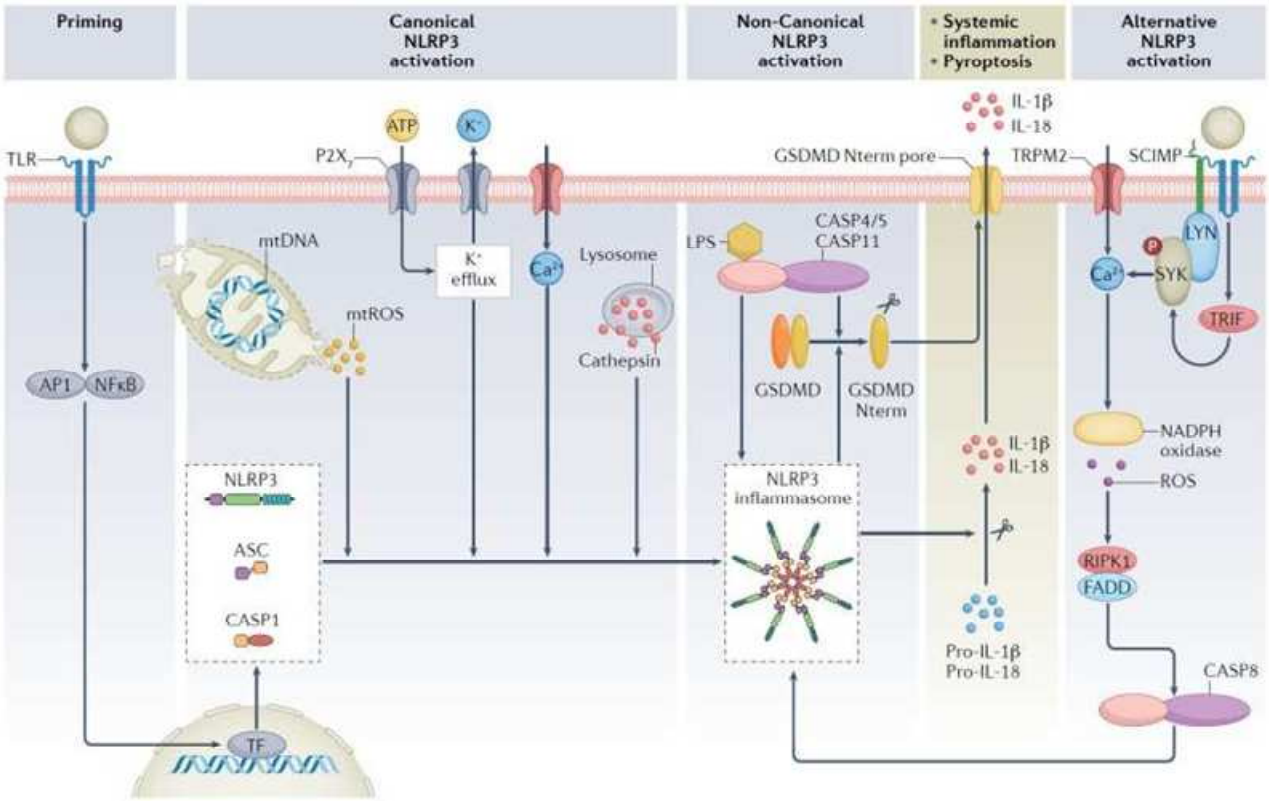
Potential of cannabidiol in diseases connected to inflammation Academic research has demonstrated in numerous *in vitro* and *in vivo* preclinical studies that cannabidiol exerts anti-inflammatory activity. According to Rajesh *et al*.'s 2010 publication, many preclinical studies have shown the potential efficacy and protective effect of cannabidiol in diseases connected to inflammatory processes. Remarkably, besides inflammation in a variety of diseases, cannabidiol attenuated myocardial dysfunction, cardiac fibrosis, inflammation, oxidative/nitrative stress, cell death and interrelated signalling pathways in heart diseases. Up until 2016, 80 clinical trials had investigated the effects of cannabidiol in various diseases such as inflammatory bowel disease and graft versus host disease (source: Lee *et al*., 2016). While the mode of action of cannabidiol's anti-inflammatory activity is not completely understood, there is a growing body of evidence on the potential inhibitory action of cannabidiol on NLRP3 and other inflammasomes, leading to their potent anti-inflammatory effects.

Inflammasome pathways play an important role in the inflammation process Inflammasomes are large, intracellular, multiprotein complexes that play a pivotal role in triggering inflammation. The term "inflammasome" was originally established by Martinon *et al*. in 2002, describing the assembly of structures in activated immune cells, which lead to the activation of proinflammatory caspases and cytokines, leading to a systemic immune response and an inflammatory form of programmed cell death referred to as pyroptosis. Pyroptosis uses a peculiar indirect killing mechanism whereby cell swelling and membrane rupture happens. The pathogens stay trapped within the host cell while recruited neutrophils and macrophages kill the pathogens. Inflammation is a natural biological response of the body's immune system to infection (i.e. pathogen-associated molecular patterns - PAMPs) or injury (i.e. cell damage-associated molecular patterns - DAMPs). PAMPs and DAMPs are the keys to inflammasome activation. When sensor caspase enzymes such as canonical (established pathways with standard features) caspase-1 or non-canonical caspase-4 and caspase-5 detect PAMPs or DAMPs, they activate pyroptosis and the subsequent release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and/or interleukin-18 (IL-18). These cytokines continue the inflammatory signalling cascade and recruit immune cells to fight infections or heal injuries. Cytokines can be divided into several types, including interleukins (ILs) ILs, colony-stimulating factors (CSFs), interferons (IFNs), tumour necrosis factors (TNFs), transforming growth factors (TGFs), chemokines, lymphokines and monokines. Excessive inflammatory cytokine production can lead to tissue damage, hemodynamic changes (i.e. instability in heart and blood flow), organ failure and ultimately death.

NLRP3 is one of the most studied inflammasomes due to its critical role in several inflammatory diseases Given the potency of inflammasome-driven immune responses, their dysregulation (i.e. aberrant inflammasome activation) is associated with excessive and self-perpetuating inflammation, which is present in most types of inflammatory diseases (e.g. autoinflammatory disorders, cardiometabolic diseases, cancer and neurodegenerative diseases). Academic evidence regarding the structural mechanisms of some inflammasomes, including NLRs inflammasomes such as NLRC4, NLRP3 and other NLRPs, as well as AIM2 and IFI16 inflammasomes, has expanded rapidly in the last decade. NLRP3, also known as cryopyrin, is by far the most thoroughly studied NLR. NLRP3 is a protein expressed by various cells, including neutrophils, macrophages, microglia, lymphocytes, epithelial cells, osteoblasts, neurons and dendritic cells (sources: Rada *et al*., 2014; Zahid *et al*., 2019). Signals that activate NLRP3 include PAMPs (e.g. toxins from bacteria, viruses and fungi) and DAMPs. Oxidative stress in the form of mitochondrial reactive oxygen species (mROS) has also been widely implicated in NLRP3 activation (sources: Duncan *et al*., 2009; Gross *et al*., 2009, Ichinohe *et al*., 2010, Toma *et al*., 2010; Schroder and Tschopp 2010, Shimada *et al*., 2011 and 2012).

There are currently a few FDA-approved drugs that target the downstream increase in pro-inflammatory cytokines resulting from aberrant activation of the NLRP3 pathway such as anakinra (Kineret®), rilonacept (Arcalyst®), and canakinumab (Ilaris®). According to the FDA-approved prescribing information, the precise mechanisms by which Epidiolex® exerts its anticonvulsant effect in humans are unknown; however, preclinical evidence suggests cannabidiol reduces the neuronal hyperexcitability of epilepsy through a unique multimodal mechanism of action (source: Nichol *et al*., 2011).

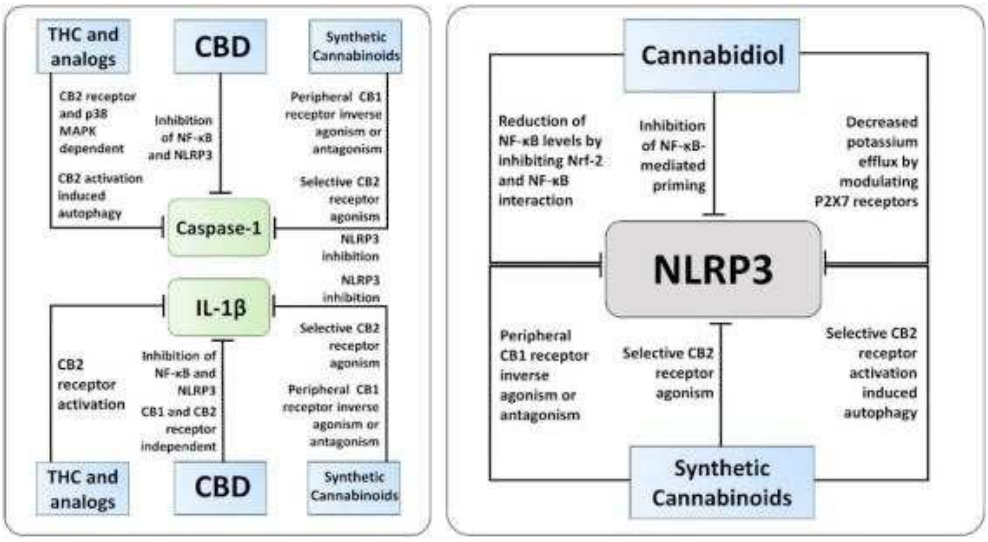
Figure 3: Pathways leading to activation of the NLRP3 Inflammasome



Source: Speer T, Dimmeler S, Schunk SJ, Fliser D, Ridker PM. Targeting innate immunity-driven inflammation in CKD and cardiovascular disease. Nat Rev Nephrol. 2022;18(12):762-778.

Preclinical research suggests that cannabidiol is a key regulator of NLRP3 Several preclinical investigations have shown that cannabidiol modulates NLRP3 activation. An Italian *in vitro* study in a human gingival mesenchymal stem cell model discovered that cannabidiol suppressed NLRP3, caspase-1 and IL-18, avoiding the risk of inflammatory reactions and promoting survival (source: Libro *et al*., 2016). An animal model in mice fed with a high-fat, high-cholesterol diet for 8 weeks showed significantly higher expressions of NLRP3 inflammasome pathway proteins NLRP3, IL-1β, and caspase-1 in the liver. These proteins were substantially reduced/attenuated by simultaneous treatment with cannabidiol administered 5 mg/kg/day for 8 weeks. The positive cannabidiol effect was confirmed by the researchers in an *in vitro* mouse macrophage cell line model (source: Huang *et al*., 2019). Similar results were obtained in different *in vivo* and/or *in vitro* neuroinflammation, colitis, multiple sclerosis or skin inflammation models (source: Suryavanshi *et al*., 2020). We give an overview of cannabidiol's known pathways of inhibition of caspase-1, IL-1β and NLRP3 in figure 4 overleaf.

Figure 4: Cannabidiol's activity on the NLRP3 inflammasome pathway



Source: Suryavanshi et al., 2020

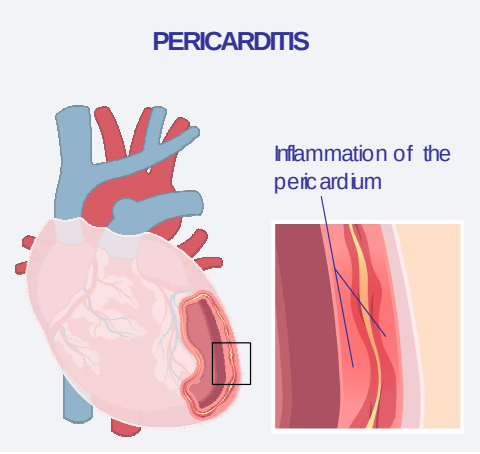
Certain cardiac diseases show a strong inflammatory component PAMPs or DAMPs in the heart usually trigger highly specific immune responses that are mediated by B and T cells accompanied by inflammation. In some cases, the inflammatory response can become dysregulated, leading to myocardial (i.e. myocarditis or heart muscle inflammation) or pericardial (i.e. pericarditis or inflammation of the protective, fluid-filled sac surrounding the heart) damage or even heart failure (i.e. the heart is unable to pump blood around the body as well as it should). The first link between inflammation and heart failure was identified by Levine *et al* in 1990. He discovered higher levels of TNF-cytokines in patients with heart failure (HF) and a reduced ejection fraction (EF - amount of blood the left ventricle of the heart pumps out to the body with each heartbeat). Recent studies of human heart tissue from people with HF conditions have revealed expression of Caspase-1 (responsible for the production of the proinflammatory cytokines IL-1β, IL-18 and TNF) and NLR inflammasome family members NLRP2 and NLRP3. These inflammasomes play an essential role in the inability of the myocardium to restore homeostasis, coupled with sustained inflammatory response and adverse cardiac remodelling (sources: Mann *et al*., 2015 and 2011). As a result, members of the IL-1, IL-6 and TNF family are key inflammation biomarkers approved by the Food and Drug Administration (FDA) for prognosis in heart failure.

ORAL CARDIOLRX™ IN RECURRENT PERICARDITIS (RP)

RP – A COMPLEX DISORDER WITH LIMITED TREATMENT OPTIONS

Description of pericarditis and RP Pericarditis refers to a common disorder characterised by inflammation of the pericardium (and development of fluid in the pericardium), a sac-like structure with two thin layers of tissue that surround the heart to hold it in place and help it work. The pericardium provides mechanical protection for the heart and lubrication to reduce friction between the heart and surrounding structures. In a healthy heart, a small amount of 15-50mL serous fluid keeps the layers separate, leading to less friction between them as the heart beats. The most common symptom of pericarditis is severe sharp chest pain, typically caused by the sac's layers becoming inflamed and possibly rubbing against the heart. Acute pericarditis is an overall benign and self-limiting disease. However, in some cases, complications may occur, and inflammation can be accompanied by increased fluid accumulation within the pericardial sac, forming a pericardial effusion. This may progress to heart failure or even death if it starts putting pressure on the heart, preventing it from pumping enough blood to the body (e.g. cardiac tamponade, recurrent pericarditis). Based on the duration of the condition, pericarditis is defined as acute if it lasts for <4-6 weeks, incessant if it lasts between 4-6 weeks and 3 months or chronic if it lasts for >3 months. Recurrent pericarditis denotes when a subject develops pericarditis for a second time after being symptom-free for at least 4-6 weeks. Recurrent pericarditis is a complex inflammatory disorder and often causes debilitating chest pain, physical limitations, hospitalisations and decreased quality of life. Pericarditis can have multiple causes. However, infections (i.e. viruses and bacteria) are responsible for 80-90% of cases. Noninfectious causes include systemic inflammatory diseases (e.g. lupus or rheumatoid arthritis), cancer and post-cardiac injury syndromes (sources: Emazio *et al*., 2015; Dababneh *et al*., 2022; Mayo Clinic).

Figure 5: Pericarditis



Source: First Berlin Equity Research, Cardiol Therapeutics Inc

Incidence and prevalence of RP Pericarditis is most common in 16 to 65-year-old men, but it can affect anybody at any age. In the Western World, the incidence of acute pericarditis is estimated at ~27.7 per 100k subjects per year. The hospitalisation rate for pericarditis is 3.32 cases per 100k persons per year (source: Lazarou *et al*., 2022). According to the European Medicines Agency, pericarditis affected approximately 2.5 in 10k people in the European Union (EU), equating to 130k people. In the US, an estimate using national health encounter surveillance databases arrived at an average of ~125k patients p.a. with pericarditis and an annualised prevalence estimate of 40 in 100k (source: Allen Luis *et al*., 2022). Recurrent pericarditis affects ~30% (15-50%) of people with acute

pericarditis in the US, or ~40k people. The rate and number of people affected with RP are well below the ceiling of 5 in 10k people in the EU and 200k patients in the US required to obtain an orphan drug designation. In addition, ~25-50% of patients who have experienced a first recurrence will experience additional recurrence, and from the patients who have experienced ⩾2 recurrences, 20-40% are expected to have further episodes. Recurrences are often the result of inadequate response to conventional therapies (sources: American Heart Association, Cremer PC *et al*., 2016; Katinaitė *et al*., 2017).

Healthcare burden The mean annual health care cost for treating hospitalised pericarditis patients in the US was estimated between USD 10k (according to a Medicare study) and USD 39k (according to a study using the US Nationwide Inpatient Sample – NIS) in 2012, whereby hospitalisation rates were at 5-26 per 100,000 people per year (source: Klein *et al*., 2022).

Diagnosis The diagnosis of pericarditis is made upon the appearance of symptoms and is based primarily on physical examination by the physician, followed by the conduct of several tests. If a subject shows the common sharp chest pain symptom, auscultation would likely reveal a pericardial friction rub produced by the two layers of the pericardium rubbing against each other. When present, to confirm the diagnosis, doctors will usually conduct an electrocardiogram (ECG), and selected laboratory tests to check for signs of inflammation and infection through biomarkers such as erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), high white blood cell count – (leukocytosis). To find more evidence of pericardial inflammation and evaluate the patient's condition and disease severity, physicians use imaging tools such as chest radiography, echocardiogram (ultrasound), cardiac computerised tomography (CT) scan or cardiac magnetic resonance imaging (MRI). The guidelines from the European Society of Cardiology (ESC) from 2015 support using advanced imaging techniques to obtain more detailed information (sources: ESC guidelines, 2015, Xanthopoulos *et al*., 2017).

Treatment of pericarditis The mainstay of pericarditis treatment in the US and Europe is the administration of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen to relieve pain and inflammation. In addition, the drug colchicine is also recommended as adjuvant therapy to ameliorate the initial episode (i.e. reduces by ~50% symptoms at 72 hours) and is associated with ~50% lower recurrence rates at 18 months when it is administered together with NSAIDs. The use of colchicine in acute pericarditis is chiefly supported by two studies, COPE (2005) and ICAP (2013), which proved a strong effect in the reduction of recurrences. ICAP was a double-blinded, placebo-controlled trial in 240 acute pericarditis patients. The use of colchicine in recurrent pericarditis was proved in three studies, CORE (2005), CORP (2011) and CORP-2 (2014), with a nearly 50% reduction in incidence of further pericardial flares in treated patients. Colchicine is associated with dose-dependent gastrointestinal side effects (mostly diarrhoea) in about 8–10% of patients. Colchicine is a drug extracted from the colchicum autumnale plant, one of the most ancient anti-inflammatory medications still used nowadays. Its primary mechanism of action relies on the inhibition of tubulin polymerization and inflammasomes (source: Emazio *et al*., 2015; Bouabdallaoui *et al*., 2020).

Corticosteroids are the second-line therapy for patients who do not respond, are intolerant or have contraindications to NSAIDs and colchicine. Corticosteroids typically provide rapid relief of symptoms in the treatment of acute and recurrent pericarditis. However, corticosteroids tend to favour the chronic evolution of the disease, promote drug dependence, and potentially lead to steroid-related side effects such as weight gain and muscle loss. They have been associated with an increased risk of recurrence (RR = 2.89 times the risk of having the recurrence when compared with the untreated group), with a dose-dependent effect. In the COPE trial, steroid use was an independent risk factor for recurrence (sources: Shabetai *et al*., 2005, Imazio *et al*., 2005 and 2008). Therefore, experts

recommend administering lower doses of corticosteroid, such as 0.2–0.5mg/kg daily of prednisone, instead of the standard effective dose of 1.0 to 1.5 mg/kg. Depending on the patient's response, a triple therapy consisting of a combination of NSAIDS + colchicine + corticosteroids can be considered (sources: Tombetti *et al*., 2020; Lo Presti *et al*., 2021; Del Pinto, 2021; Kumar *et al*., 2023; ESC guidelines 2015).

The third-line therapy for recurrent pericarditis patients not responding to NSAIDs, colchicine and corticosteroids (about 5% of patients) include the immunosuppressive drugs methotrexate, intravenous immunoglobulins (IvIG) and azathioprine. However, there is limited clinical evidence for their administration. They are primarily used as steroid-sparing agents or to treat any identified underlying auto-immune disease (sources: Lo Presti *et al*., 2021; Del Pinto *et al*., 2021; Kumar *et al*., 2023).

Third-line treatments – IL-1 inhibitors Therapeutic options that target the downstream increase in pro-inflammatory cytokines resulting from aberrant activation of the NLRP3 pathway include the anti IL-1 compounds rilonacept (Arcalyst® from UK-based Kiniksa Pharmaceuticals), anakinra (Kineret® from Amgen in the US, Swedish Orphan Biovitrum - SOBI has ex-US rights) and canakinumab (Ilaris® from the Swiss-based Novartis).

Rilonacept (Arcalyst®) injection - since 2021, the only US-approved drug for the treatment of recurrent pericarditis (RP) Rilonacept is a fusion protein capable of binding to and neutralising the pro-inflammatory cytokines IL-1β and IL-1α. The drug was approved for the treatment of the rare hereditary inflammatory disorder Cryopyrin-associated periodic syndrome (CAPS) in 2008 and has been approved for recurrent pericarditis since 2021. The US approval for recurrent pericarditis was granted based on the global, double-blind, randomised phase III RHAPSODY (Study to Assess the Efficacy and Safety of Rilonacept Treatment in Participants With Recurrent Pericarditis) trial in 86 patients led by Dr Allan Klein at the Cleveland Clinic. The drug's efficacy, defined as patients with no or minimal pericarditis symptoms after 16 weeks of treatment, was 81% vs 25% in the placebo group. The drug also decreased recurrences by 96% (rilonacept 7% versus placebo 74%; P<0.001). Besides rilonacept, there is no other FDA-approved therapy for pericarditis in patients not responding to NSAID's, colchicine or corticosteroids. Rilonacept is a biologic drug with a high retail price of about USD 20k per month, according to the American College of Cardiology, Nov. 2022. Cardiol estimates the product's price at >USD 200k p.a. or >USD 150k after discounts. It has a half-life of 7 days (sources: Lo Presti *et al*., 2021; press release Cleveland University, 2021). Riloncept is not approved in Europe.

Anakinra (Kineret®) injection is approved in the US for rheumatoid arthritis (RA) CAPS and deficiency of IL-1 receptor antagonist (DIRA) - it has off-label use in RP Anakinra was the first IL-1 inhibitor to be developed, blocking the cytokines IL-1β and IL-1α. The drug was approved in the US for the treatment of RA in 2001, for CAPS in 2013 and treatment of the ultra-rare autoinflammatory disease DIRA in 2020. The compound was studied in the AIRTRIP (Anakinra Treatment of Recurrent Idiopathic Pericarditis) trial, a randomised, double-blinded, placebo-controlled trial conducted on 21 patients in Italy in 2015. At the end of the study, the patients treated with anakinra showed a significantly lower RP incidence of 18.2% vs 90% in the placebo group (P=0.001). Based on these results, anakinra currently represents a valid option for off-label use in RP. Since 2015, SOBI has not taken steps to conduct a registration study for this indication. Similarly to rilonacept, a main limitation on its wider use is its high price. Also, anakinra's short plasma half-life of 4–6h is a compliance shortcoming among patients due to required daily subcutaneous injections (sources: Lo Presti *et al*., 2021; Granowitz *et al*., 1992).

Canakinumab (Ilaris®) injection is approved for CAPS, juvenile arthritis and AOSD Canakinumab is an anti-IL-1β monoclonal antibody approved for CAPS in 2009, juvenile idiopathic arthritis in 2013, rare periodic fever syndromes in 2016, and adult-onset Still's disease (AOSD) in 2020. We believe this drug plays the least relevant role in the potential treatment of RP. There is little data on its potential efficacy in RP, which is chiefly limited to case series (study of a few single patients) with mixed results. Its price is also very high. However, at 26 days, Canakinumab has the best half-life among the three approved IL-1 inhibitors.

Table 7: Overview of the three most advanced IL-1 inhibitors for RP

	Anakinra (Kineret®)	Rilonacept (Arcalyst®)	Canakinumab (Ilaris®)
Formulation	Recombinant human IL-1Ra	IL-1α and IL-1β trap	Human monoclonal antibody anti-IL-1β
IL-1 target	IL-1α and IL-1β	IL-1α and IL-1β	IL-1β
Half-life	4–6 h	7 days	26 days
Administration	Subcutaneous or intravenous	Subcutaneous	Subcutaneous
Dosing	Every day	Weekly	Every 1–2 months
Anti-inflammatory potency	+++	++	+++
FDA-approved indications	CAPS, RA	CAPS, RP	CAPS, TRAPS, FMF, HIDS/MVK, systemic juvenile IA, adult-onset Still disease
Adverse events	Injection site reactions (ISR), hepatitis, infections	ISR, infections, neutropenia, hyperlipidemia	ISR, infections, neutropenia
Therapy duration in pericarditis	3–6 months (usual), longer times in specific cases	At least 6–8 months	At least 6–12 months

Source: Imazio et al., 2021

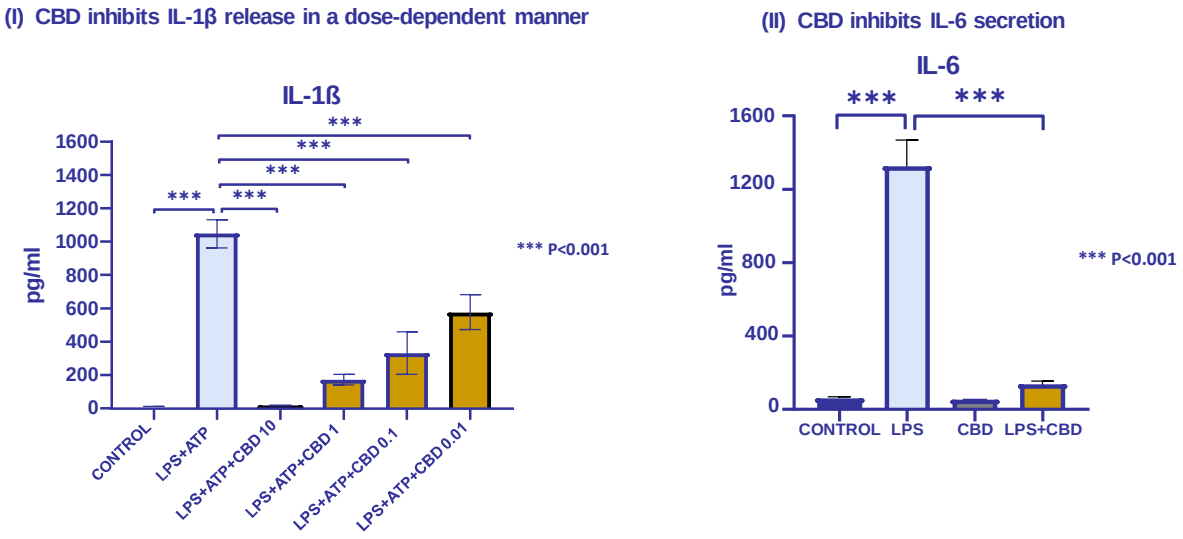
Next wave of RP drugs candidates- CardiolRx™ leads the race showing potential as first-line therapy, the IL-1 inhibitor goflikicept may be a future second alternative to Rilonacept (Arcalyst®) Overall, there is a significant unmet medical need for the treatment of RP, given that there is only one approved drug, which is used as third-line therapy in the treatment of the disease. CardiolRx™, which appears to work by attenuating multiple inflammatory signalling pathways, including inhibiting activation of the NLRP3 inflammasome, is currently undergoing a pilot phase II study in RP. Cardiol's intend is that CardiolRx™ could be the first drug approved as a first-line therapy for RP. Given the growing efficacy evidence of IL-1 inhibitors in patients with corticosteroid-dependent colchicine-resistant recurrent pericarditis, we expect that further products may emerge from this class. It is difficult to predict if anakinra (Kineret®) may still pursue a registration trial in the future; SOBI is currently busy with other indications. The Turkish company TRPHARM is developing goflikicept - RPH-104, a recombinant human IL-1-receptor antagonist targeting the cytokines IL-1α and IL-1β. The drug candidate is in phase II-III in recurrent pericarditis. Preliminary data from the 20 randomised patients reported at the EULAR Conference in June 2022 showed that recurrent pericarditis occurred in 8 of 10 patients in the placebo group, but there were no recurrence events in the goflikicept group at the time of the interim analysis. The assessment was conducted in January 2022 (source: Abstract from the EULAR Conference 2022, clinicaltrials.gov – trial NCT04692766). At present, we have not identified further programmes in an advanced development stage for RP.

Pericarditis treatment market to show a healthy growth dynamic in the period 2022-2032 The global pericarditis drugs market was valued at USD 3.6bn in 2022 and is expected to reach USD 6.0bn by 2032, expanding at a CAGR of 5.2% in the period (source: Future Market Insights, 2022). This can be attributed to the rising prevalence of cardiovascular diseases, new product launches (i.e. rilonacept (Arcalyst® and potentially other IL-1 inhibitors, CardiolRx™, etc.) and demand for these premium-priced drugs.

PRECLINICAL STUDY SHOWS PROTECTIVE ACTIVITY OF CANNABIDIOL IN PERICARDITIS

***In vitro* study: pharmaceutically manufactured cannabidiol inhibited the pro-inflammatory cytokines IL-1β and IL-6,…** Cardiol Therapeutics recently generated new data studying the influence of its cannabidiol compound in a preclinical model of acute pericarditis, presenting the exciting results at the American Heart Association Scientific Sessions 2022. The company's research collaborators from Virginia Commonwealth University (VCU) used a well-established *in vitro* model of murine macrophages, stimulating them with lipopolysaccharide (LPS – a well-known PAMP expressed on Gram-negative bacteria) and/or adenosine triphosphate (ATP – is typically released by bacteria / host cells during bacterial infection), to activate the NLRP3 inflammasome and thereby simulate an inflammatory environment as a testing model. The VCU research team conducted two separate experiments, adding to the cell lines A) LPS+ATP and B) LPS alone, comparing both with and without cannabidiol addition. The scientists measured the concentration of the inflammatory cytokines IL-1β and IL-6 via an ELISA assay. In A), the LPS+ATP combination increased IL-1β concentration to 449.1 pg/mL vs control 6.4 pg/mL ($p<0.0001$). The addition of cannabidiol significantly reduced IL-1β concentration to 118.7 pg/mL with a statistical significance of $p<0.0001$. Furthermore, the IL-1β reduction was clearly cannabidiol dose-dependent ($p<0.0001$), as can be seen in figure 7-part (I). In B), LPS alone significantly increased IL-6 concentration, and that effect was almost cancelled with cannabidiol application. The VCU scientists observed that IL-6 release induced by LPS was independent of NLRP3 activation, which suggests that cannabidiol's anti-inflammatory activity is not connected only to the NLRP3 inflammasome pathway. We give an overview of the results in figure 7.

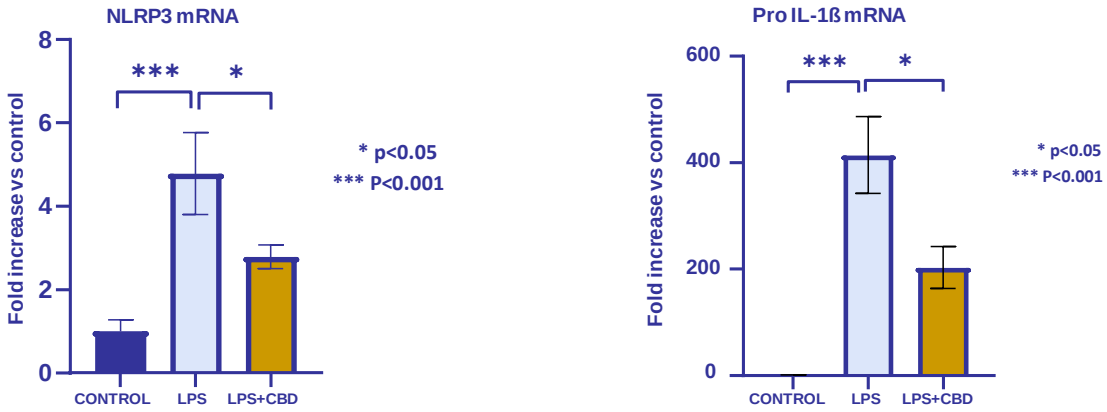
Figure 7: Cannabidiol (CBD) inhibits release of (I) IL-1β and (II) IL-6 in a murine macrophage inflammation model



Source: First Berlin Equity Research, Cardiol Therapeutics Inc

…and the inflammasome NLRP3 The VCU scientists additionally investigated gene expression using real-time polymerase chain reaction (PCR), looking for IL-1β and NLRP3 messenger RNA following LPS addition to the macrophage cell lines. As illustrated in figure 8, LPS significantly increased the transcription of NLRP3 and IL-1β, but the administration of cannabidiol significantly reduced their transcription level.

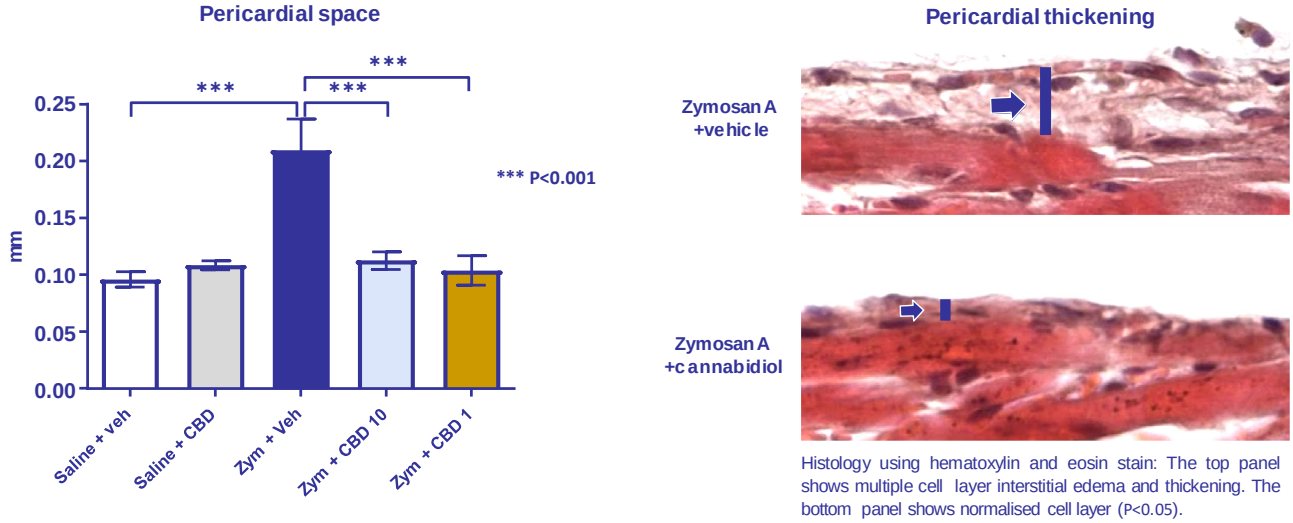
Figure 8: Cannabidiol (CBD) lowered the transcription of NLRP3 and IL-1β measured by mRNA expression



Source: First Berlin Equity Research, Cardiol Therapeutics Inc

***In vivo* study: cannabidiol reduced Zymosan-induced acute pericarditis** To confirm the *in vitro* results, the VCU research team investigated the effect of cannabidiol in a mouse model, inducing pericarditis through the intrapericardial injection of zymosan**.** Zymosan is an established reagent that can cause an intense inflammatory response and is being newly used in experimental modelling of acute pericarditis in mice (source: Mauro *et al*., 2021). Pericarditis results from inflammation of the pericardium, characterised by pericardial effusion (build-up of fluid in the pericardium) and thickening. The *in vivo* study was randomised, with one group receiving intraperitoneal injections of cannabidiol and the other vehicle control (placebo). Pericarditis severity was assessed by the presence of effusion via echocardiography (measured as width of pericardial space) and pericardial thickening. After 7 days, the cannabidiol group had significantly reduced pericardial effusion to 0.12mm vs 0.26mm for the control group (p<0.01). Pericardial thickness in the cannabidiol-treated group was also lower, with 3.6µm vs 6.5 µm for the control group (p<0.05).

Figure 9: *In vivo* acute pericarditis study established cannabidiol's (CBD) efficacy based on imaging-assessed effusion and thickening



Histology using hematoxylin and eosin stain: The top panel shows multiple cell layer interstitial edema and thickening. The bottom panel shows normalised cell layer (P<0.05).

Source: Cardiol Therapeutics Inc

The positive results provide a solid scientific basis for the clinical development of CardiolRx™ as a potential novel therapy in recurrent pericarditis treatment. The company has filed comprehensive patent applications in the US concerning these new findings.

PHASE I CLINICAL DEVELOPMENT

Comprehensive phase I randomised, placebo-controlled, double-blind dose-escalating study in 52 healthy volunteers to investigate the compound's safety and pharmacokinetics A first-in-human phase I clinical trial to determine oral CardiolRx™'s safety and tolerability as well as the pharmacokinetics profile (blood levels of the compound) was conducted in 52 healthy subjects (age: 25 - 60 years). The volunteers were randomised to one of two groups to compare the drug's once-a-day (QD) dosing against twice-a-day (BID) dosing in either a fed or fasted state administered for six days:

- The QD dose was tested in Group A, split into three sub-groups, each involving 12 subjects (9 CardiolRx™ and 3 placebo). Each subject received a single dose of 5 mg/kg or 15 mg/kg of CardiolRx™.
- The BID dose was tested in Group B, split into two sub-groups, each involving 8 subjects (6 CardiolRx™ and two placebo). Each subject received BID administration of CardiolRx™ with doses of 5 mg/kg or 15 mg/kg.

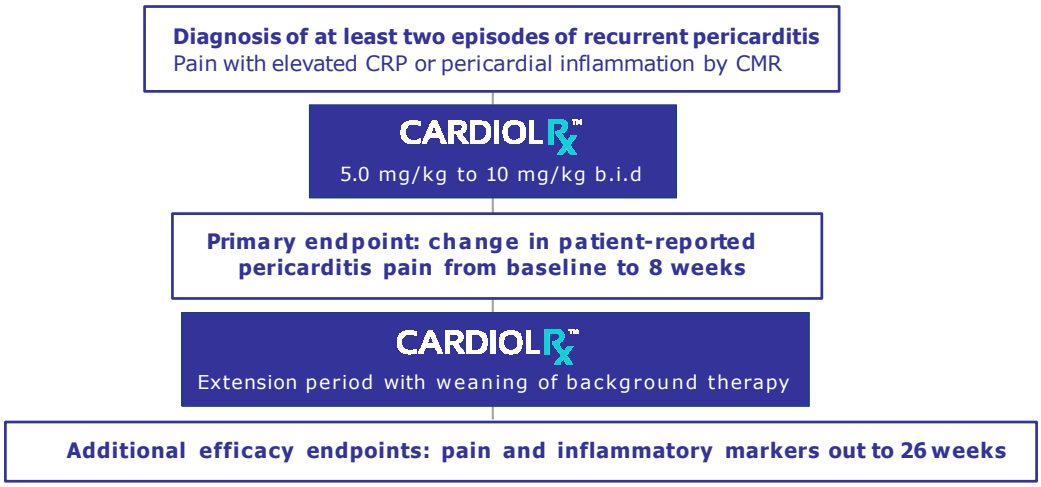
CardiolRx™ was safe and generally well tolerated at all dose levels; fed state administration delivered 6-7x higher drug concentration in blood Despite the relatively high doses of CardiolRx™ administered in the phase I study, there were no abnormal electrocardiogram (e.g. heart problems) or laboratory findings (e.g. elevated liver enzymes). The reported adverse events were all mild or moderate and were primarily related to the gastro-intestinal tract. The pharmacokinetic headline results showed a dose-dependant blood concentration level of CardiolRx™ in blood, and this performance was 6-7x higher in the fed state vs the fasted state. This finding was anticipated, considering cannabidiol's intrinsic fat solubility characteristic. Also, the QD administration of CardiolRx™ in fed state showed a time to maximal blood level (Tmax) of 5-7 hours, with a half-life of 26-29 hours. These findings suggest that BID should be the recommended administration regimen for the coming phase II studies.

PILOT PHASE II CLINICAL STUDY IN RP

US phase II pilot trial aims to assess the efficacy and safety of CardiolRx™'s BID administration in recurrent pericarditis patients The study protocol, designed with the active participation of pericardial disease opinion leaders, entails a US, open-label, multi-centre phase II pilot trial to assess the efficacy, safety and tolerability of CardiolRx™ in patients with recurrent pericarditis. The patients will be treated for 8 weeks with BID drug doses escalating from 5 mg/kg at the beginning of the study to 10.0 mg/kg towards the end of the treatment period. Then, the patients will undergo a 26-week extension treatment period with progressive weaning of concomitant background therapy, including corticosteroids, to investigate CardiolRx™'s activity as a stand-alone drug. The study will take place in 5-10 major specialised centres.

Primary efficacy endpoint to be measured through NRS pain scale The primary efficacy endpoint is the change from baseline over 8 weeks in patient-reported pericarditis pain intensity using an 11-point numeric rating scale (NRS). The NRS pain screening tool is widely used in clinical settings to assess pain severity using a 0–10 scale (0= no pain and 10= the worst pain imaginable) in multiple conditions associated with acute and chronic pain, including previous studies of recurrent pericarditis. Secondary endpoints include the NRS pain score after 26 weeks of treatment and changes in circulating levels of C-reactive protein (a relevant marker of inflammation). We give an overview of the pilot phase II recurrent pericarditis study design in figure 10 overleaf.

Figure 10: Overview of the pilot phase II recurrent pericarditis study design



Source: First Berlin Equity Research, Cardiol Therapeutics Inc

Pilot phase II study started in December 2022; headline data should be available in early 2024 On 17 January 2023, the company enrolled the first patient of CardiolRx™'s pilot study at the Cleveland Clinic. Further US centres are being recruited. Management anticipates that this study will last about 12 months. We expect to see headline results in early 2024.

CardiolRx™ is replicating the fast registration pathway of rilonacept (Arcalyst®), which maximises success chances and lowers the development/registration risk The Chairman of CardiolRx™'s phase II study is Dr Allan L. Klein, MD, Director of the Centre of Pericardial Diseases and Professor of Medicine, Heart and Vascular Institute, at the Cleveland Clinic. Importantly, Dr Klein was the lead investigator of the pivotal trial of the rilonacept (Arcalyst®) injection, the first and only FDA-approved therapy to treat recurrent pericarditis (approved in March 2021). He is a pericarditis expert who knows how to run a trial mastering the FDA registration requirements successfully. Cardiol's registration pathway is the same as Kiniksa Pharmaceuticals', which first conducted a pilot open-label study in 25 patients followed by the phase III pivotal RHAPSODY study in 61 patients. Kiniksa completed this development process within a record time of only ~3 years: phase II took ~1.5 years, and phase III took ~2 years with an overlap of ~6 months. Kiniksa started the phase II trial in January 2018 and reported positive interim data in 12 patients in December 2018. Based on this, the FDA allowed the company to initiate the phase III study in January 2019. The company completed the phase II study in May 2019 and the phase III study in November 2020 and received the FDA's drug approval in March 2021. The market launch took place in April 2021. Cardiol is pursuing this proven registration strategy to maximise success chances and lower development and registration risks. Due to the potentially fast registration path and the promising success chances, this program is Cardiol's first priority (sources: Cardiol Therapeutics, Klein *et al.*, 2021; ClinicalTrials.gov Identifiers: NCT03980522 & NCT03737110; Kiniksa press releases; Cleveland Clinic).

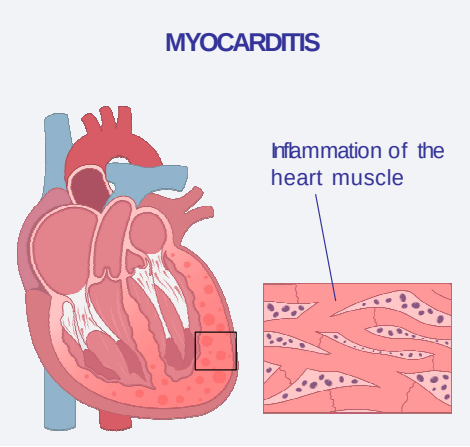
Phase III study could start in H1 2024 – we conservatively anticipate a potential drug approval and market launch in H2 2026 Assuming the pilot study is successful, we expect that a pivotal phase III study will require enrolling ~50-70 patients (vs rilonacept/Arcalyst®'s phase III with 61 patients). In this scenario, we expect the phase III study to start in H1 2024 and deliver results by H1 2026. Assuming orphan drug and fast-track designations, we project a potential drug approval and market launch in the US in H2 2026.

ORAL CARDIOLRX™ IN ACUTE MYOCARDITIS (AM)

AM IS A DISEASE WITH HIGH UNMET MEDICAL NEED

Description of acute myocarditis Myocarditis is an uncommon, potentially life-threatening inflammatory disease of the myocardium, the middle and thickest muscular layer of the heart. The main function of the myocardium is to facilitate the contraction (heartbeat) and relaxation of the heart walls to pump blood into systemic circulation and receive it back. Myocarditis is caused predominantly by viruses (e.g. influenza, SAR-CoV2, herpes, measles, hepatitis C viruses, HIV), but also other infecting agents such as bacteria (e.g. Borrelia) or fungi, general inflammatory conditions, or exposure to toxic substances or drugs (e.g. cancer drugs such as chemotherapeutic agents and immune checkpoint inhibitors, antipsychotics, antibiotics, and vaccines including COVID-19 -vaccines). A typical myocarditis case can manifest with chest pain occurring 1-2 weeks after a viral infection of the upper respiratory or gastrointestinal tract. Still, in many cases (about 50%), no specific underlying cause for the inflammation can be identified (idiopathic). The inflammation in myocarditis can reduce the heart's ability to pump blood, triggering typical symptoms such as chest pain (85–95% of cases), shortness of breath (19–49% of cases), fatigue, and rapid or irregular heart rhythms (arrhythmias). Myocarditis has a wide spectrum of clinical outcomes, with most cases showing either no or mild symptoms and resolving spontaneously or through medication. However, in some patients, persistent myocardial inflammation may cause extensive muscle tissue damage and scarring that triggers left ventricular (LV) remodelling, leading eventually in up to 30% of cases to dilated cardiomyopathy (DCM – it is a leading cause of cardiac transplantation), acute and fulminant heart failure or even sudden cardiac death (sources: Mayo Clinic; Al-Akchar *et al*., 2022; Lampejo *et al*., 2021; Dominguez *et al*., 2016; Ammirati *et al*., 2018).

Figure 11: Acute myocarditis



Source: First Berlin Equity Research, Cardiol Therapeutics Inc

Incidence and prevalence of AM AM is a cardiac condition affecting relatively young patients (median age of onset ranges between 30-45 years in most cases) and men more than women (male prevalence ranges between 60-80%). AM incidence is usually estimated between 10-20 cases per 100k persons. In the US, this estimate was 14.4 cases per 100k in 2014 with a growing trend (in 2005, the incidence was 9.5 per 100k). We thus see Cardiol's estimate of 16.2 cases per 100k cases for the US (based on Wang *et al*., 2021), equating to about 54k people suffering from AM, as realistic. In the EU, this incidence would represent ~72k patients p.a. Importantly, these figures are well below the ceiling of 50 in 100k people in the EU and 200k patients in the US required to obtain an orphan drug designation. Following the COVID-19 pandemic, AM's incidence may be much higher (sources: American Heart Association, 2021; Kang *et al*., 2022, Ammirati *et al*., 2021; Wang *et al*., 2021).

Diagnosis of AM Symptoms of AM, such as chest pain, are similar to the ones of other common heart disorders, such as coronary artery disease (CAD) or even pericarditis. Therefore, accurate AM diagnosis may be challenging. In the first step, the doctor will typically examine the patient's heart with a stethoscope, followed by conducting laboratory tests to confirm the diagnosis. The blood tests will look for biomarkers of inflammation (e.g. C-reactive protein and erythrocyte sedimentation rate), infection (e.g. complete blood count) and myocardial necrosis such as troponins and creatine kinase-myocardial band. Then the doctors will conduct an ECG, and several imaging tests such as chest radiography, echocardiogram (ultrasound), cardiac computerised tomography (CT) scan, or cardiac magnetic resonance imaging (MRI). The MRI is considered the gold standard non-invasive option to evaluate the disease condition (i.e. tissue characterisation, including recognition and quantification of inflammation and scar fibrosis) and its severity in patients with suspected myocarditis. The combination of a high-sensitivity troponin test + cardiac MRI provides an accurate base for a diagnosis in most cases. In certain patients with high-risk features, the gold standard for diagnosis of myocarditis is still endomyocardial biopsy (EMB) with a catheter to identify the underlying cause (e.g. infection) and the type of inflammation (sources: Mayo Clinic, Ammirati *et al*., 2021; Law *et al*., 2021).

Treatment and main products There is no cure and no approved drug for the treatment of AM. Current treatment is mainly supportive of the heart's function. These typically administered drugs can be classified into one of the following three core groups:

- **Corticosteroids** lessen the intensity of the immune response and can therefore be helpful in managing inflammation in some cases. Nevertheless, immunosuppressive therapy such as corticosteroids shows limited efficacy in AM. NSAIDs should be avoided as they may impair the healing of the myocardium (Al-Akchar *et al*., 2022).
- **Cardiac medications** help control the signs of heart failure by reducing the amount of work the heart is doing. The most commonly prescribed drugs are:
  - Beta-blockers: slow down the heart and prevent arrhythmias.
  - Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), cardiac inotropes: relax veins and arteries, lowering blood pressure.
- **Diuretics** can help reduce the body's fluid accumulation, which can occur when the heart muscle weakens, reducing the strain on the heart.

Emerging therapies – CardiolRx™ is in our view the most advanced and most promising clinical-stage programme The industry's clinical-stage development pipeline for the AM indication is thin. In our view, CardiolRx™ in phase II development is the most promising drug candidate to address this disease, for which there is no approved therapy so far. The main peer compound to watch is the IL-1α and IL-1β inhibitor Kineret® (anakinra). The AM investigator-sponsored clinical study "Anakinra Versus Placebo for the Treatment of Acute Myocarditis" (ARAMIS, see: https://clinicaltrials.gov/ct2/show/NCT03018834) in 120 patients has been quiet lately. We thus suspect results may not be as expected. The data intelligence provider Pharmaceutical Technology / Global Data estimates that the likelihood of phase transition and potential approval declined following an undisclosed event in June 2022. The next peer compound to watch is Cantargia's antibody CAN-10 which has a novel approach. It modifies the activity of the target protein IL1RAP to block IL-1, IL-33 and IL-36 signalling. The drug candidate has recently completed its toxicology studies and plans to initiate its first-to-man phase I safety study in H1 2023. The remaining AM drug candidates are in the early preclinical stage, and little information about them is available. We give an overview of the emerging AM therapies in table 8 overleaf.

Table 8: Overview of emerging therapies in clinical development for AM

Company	Drug candidate	Mechanism	Development stage	Comments
Cardiol Therapeutics (Canada)	CardiolRx™ (oral cannabidiol),	Not fully known, addresses the inflammasomme NLRP3, inhibits the inflammatory cytokines IL-1β and IL-6	Phase II study started in August 2022	The phase II ARCHER study in ~100 patients is expected to deliver results in 2024
Amgen (US) and Swedish Orphan Biovitrum (ex-US)	Kineret® (anakinra), subcutaneous or intravenous	addresses the inflammasomme NLRP3, IL-1α and IL-1β inhibitor	Phase II/III Investigator Sponsored Study started in 2017	The ARAMIS study was planned to be completed in May 2022. No news so far. According to "Pharmaceutical Technology", the likelihood of phase transition & approval has declined
Cantargia (Sweden)	CAN10, injectable antibody	modifies the activity of the target protein IL1RAP to block IL-1, IL-33 and IL-36 signaling	Late-stage preclinical	Completed toxicity study in January 2023, plans to initiate the phase I study during H1 2023
Inflamma Therapeutics (US)	IFT100, injectable antibody	inhibits NK cells	Mid-stage Preclinical	The company aims to conduct *in vivo* studies in myocarditis model, financing of the start-up is unclear
Evotec (Germany)	Peptide programmes, oral administration	Generate drugs from tick's evasins capable of binding and neutralising inflammatory chemokines	Early-stage preclinical	Technology transfer with Oxford University to generate therapeutic agents for myocarditis

Source: First Berlin Equity Research

The myocarditis market is set to achieve a high single-digit percentage rate growth The global pericarditis market is an attractive niche worth approx. USD 1.6bn in 2021, growing by a CAGR of 6.2% to achieve USD 2.6bn by 2029. The development and launch of new therapies, an increasing prevalence and a possible impact of the SARS-CoV-2 virus on prevalence will drive growth (source: Bridge Market Research, 2022).

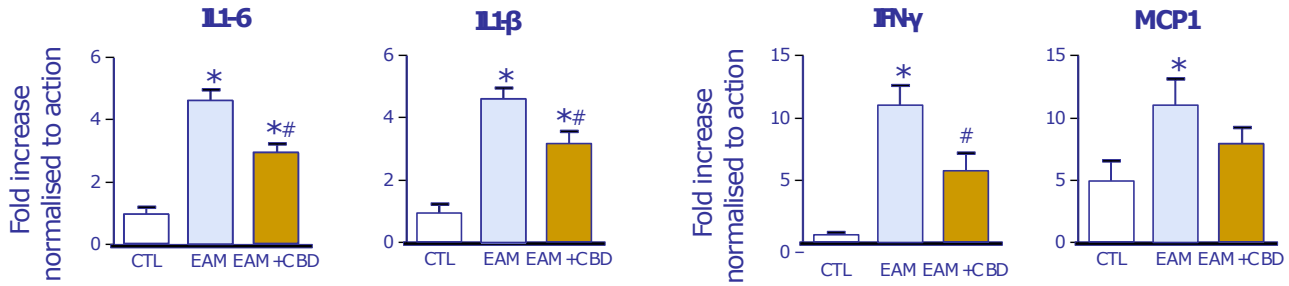
PRECLINICAL INVESTIGATION SHOWS PROMISE OF CANNABIDIOL IN ACUTE MYOCARDITIS

Preclinical study of cannabidiol's administration in a myocarditis experimental mouse model (EAM) An independent *in-vivo* study exploring the use of cannabidiol in the treatment of myocarditis, chiefly funded by the Intramural Research Program of the National Institutes of Health in the US, was completed and published by Lee *et al*. in Molecular Medicine in January 2016. This study delivered preclinical evidence of cannabidiol's benefits for myocarditis therapy. The research team used a well-established mouse model of experimental autoimmune myocarditis (EAM). Myocarditis was induced by immunisation with cardiac myosin through injection of the myocarditogenic peptide MyHCα emulsified in adjuvant. The generated EAM mouse model showed pronounced myocardial T cell-mediated inflammation and T cell infiltration, oxidative stress, cardiomyocyte necrosis (cell death), fibrosis (scars) and myocardial dysfunction. The animals were treated daily either with cannabidiol injected intraperitoneally at a dose of 10 mg/kg or with vehicle (similar to placebo).

Cannabidiol attenuates inflammation, oxidative stress and necrosis in the EAM mouse model Cannabidiol treatment largely reduced the CD3+ and CD4+ T cell-mediated inflammatory response and injury, the inflammatory cell penetration and necrosis, oxidative stress, cardiac dysfunction and myocardial stiffness in EAM mouse myocardium at day 46. Inflammation is usually associated with excessive oxidative/nitrative stress. When immune cells such as macrophages and monocytes become activated, they start producing various cytokines (e.g. overexpression of IL-6 and overactivation of IL-1 signalling) and reactive

oxygen species (ROS) and reactive nitrogen species (RNS), leading to fibrosis. Cannabidiol controls inflammation by decreasing the pro-inflammatory cytokines. As a result, cannabidiol lowered the expression of pro-inflammatory markers, including cytokines interleukin IL-6 and IL-1β, interferon IFN-γ, and the mRNA levels of chemokine monocyte chemoattractant protein MCP-1 (see figure 12 below).

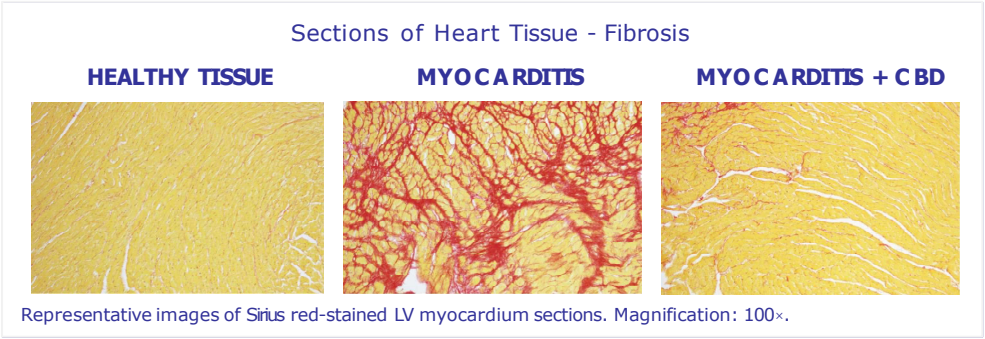
Figure 12: Cannabidiol (CBD) downregulates key inflammation cytokines (IL-6, IL-ß and IFN-γ) and chemokines (MCP1)



Source: Wen-Shin Lee et al., 2016

Cannabidiol protects against fibrotic remodelling of the myocardium in EAM The excessive level of inflammation in the EAM was associated with the extreme fibrotic remodelling of the left ventricle myocardium on day 46. Cannabidiol treatment dramatically protects the myocardium against fibrotic remodelling of the heart. Figure 13 shows a comparison in the investigation between myocardium tissue samples taken from healthy mouse tissue, EAM fibrotic tissue, and EAM tissue administered cannabidiol, visualised with Sirius red-stained (SRS) under the microscope amplified at 100x. SRS is a diagnostic azo dye (organic compound) used to observe fibrosis levels in cases of inflammation.

Figure 13: Effect of cannabidiol on heart fibrosis – experimental model of autoimmune myocarditis



Source: First Berlin Equity Research, Cardiol Therapeutics adapted from Wen-Shin Lee et al., 2016

Cannabidiol should be further investigated in clinical development The *in vivo* preclinical study provided encouraging results. Cannabidiol has attractive anti-inflammatory attributes offering potential as a promising novel treatment for managing autoimmune myocarditis and inflammatory cardiac disorders.

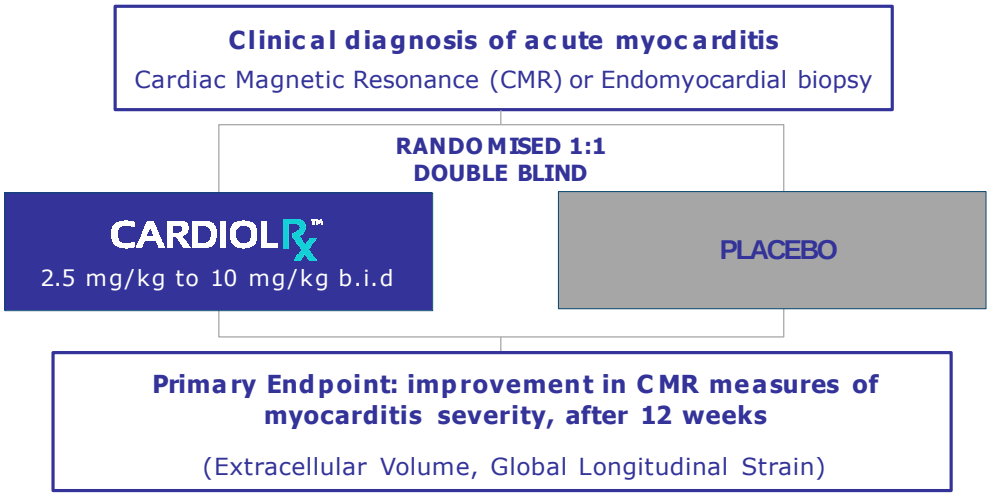
ONGOING PHASE II TRIAL OF CARDIOLRX™ IN MYOCARDITIS PATIENTS

Successful phase I study cleared the way for the phase II myocarditis study Following the successful randomised, placebo-controlled, double-blind dose-escalating study in 52 healthy volunteers demonstrating the compound's safety (see pericarditis chapter), the company was able to start a phase II study in acute myocarditis.

Proof of concept international phase II ARCHER study with 100 patients is underway Cardiol Therapeutics is conducting a phase II proof of concept study (named ARCHER) of oral CardiolRx™ in acute myocarditis patients. This planned multi-centre, double-blinded, randomised, placebo-controlled phase II trial will investigate the drug's safety, tolerability and efficacy in 100 patients at major cardiac centres in North America, Europe, Latin America, and Israel. The first patient was enrolled in August 2022.

Primary endpoint – improvement in myocarditis severity assessed by cardiovascular magnetic resonance imaging (CMR) The study design will include approximately 100 patients in total, split into two randomised arms of 50 patients each. Each arm will receive BID doses of either oral CardiolRx™ or placebo, escalating weekly over four weeks from 2.5 mg/kg to 10 mg/kg of body weight. The 10 mg/kg BID dose will be administered over the remaining 8 weeks until the full 12 weeks treatment period is completed. The primary endpoints of the trial, which will be evaluated after 12 weeks of double-blind therapy, consist of the following cardiac magnetic resonance (CMR) imaging measures: left ventricular function (global longitudinal strain) and myocardial fibrosis (extra-cellular volume fraction). These imaging parameters are robust long-term predictors of clinical outcomes in patients with acute myocarditis. The secondary endpoint is left ventricular ejection fraction also measured by CMR. Further relevant outcome measures will be the percentage of patients recovered (LVEF $\geqslant$ 0.55 at 12 weeks of treatment), changes in New York Heart Association classification and Kansas City Cardiomyopathy Questionnaire, changes in inflammatory biomarkers (e.g. hs-troponin, NT-proBNP, TNF-alpha, IL-1 beta, IL-6 (pg/mL), changes in ECG. (sources: https://clinicaltrials.gov/ct2/show/NCT05180240; Treibel *et al*., 2020).

Figure 14: CardiolRx™ phase II *ARCHER* Study Design



Source: First Berlin Equity Research, Cardiol Therapeutics Inc

The ongoing phase II study may last ~2 years and could be completed by H2 2024 or H1 2025 As of February 2023, the company has included 15 leading cardiac centres across the US (8), Canada (2) and Israel (5), and most of the centres are already actively recruiting patients. The centres' expansion is underway, and additional centres are planned to join over the coming months.

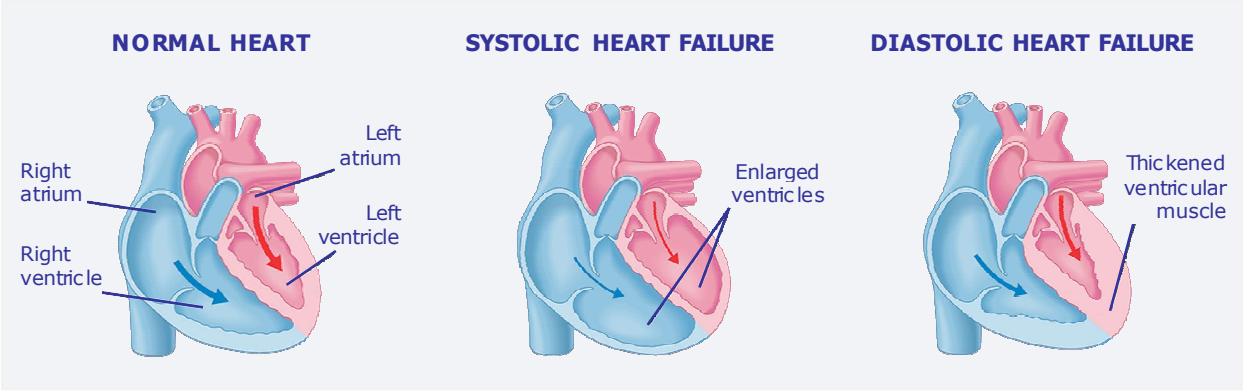
We have assumed a pivotal phase III study in ~200-300 patients over ~3-years, we project a potential drug approval and market launch in H2 2028 Assuming positive phase II results, we believe the company would negotiate and close a partnership deal. Following discussion with the regulators, preparation and approval of the protocol, the phase II/III study would start in H1 2025, leading to final data and NDA submission in H1 2028. Assuming an orphan drug and FDA priority review designation (FDA decision within six months), approval and market launch could potentially occur in H2 2028.

INJECTABLE FORMULATION FOR DIASTOLIC HEART FAILURE (DHF) IN PRECLINICAL DEVELOPMENT

DHF – A DISEASE WITH POOR TREATMENT OUTCOME

Heart failure disease CardiolRx™ is believed to have strong therapeutic potential in diastolic heart failure (DHF). Heart failure (HF) is a condition that occurs when the heart muscle, the myocardium, has functional defects hindering its strongest lower chamber, the left ventricle (LV), from pumping out sufficient blood to meet the body's needs. The percentage of blood volume the LV can eject with each heart contraction divided by the volume of blood when the LV is maximally filled is called LV ejection fraction (EF). According to the American Heart Association, a LVEF of 50-70% is categorised as normal; a preserved or mildly reduced LVEF is 41-49%, and a reduced LVEF is usually 40% or less. It is estimated that about 50% of HF people have preserved EF, and the other 50% have reduced EF. When HF with lower than normal EF happens, blood often backs up and fluid can build up in the lungs, causing shortness of breath. There are two types of LVHF: 1) systolic HF happens when the heart muscle is weak, the LV cavity is typically dilated and the LV can't contract normally - it is also called HF with reduced EF (HFrEF), and 2) diastolic HF happens when the heart muscle is stiff and thickened, and the LV can't relax normally after each contraction - it's also called HF with preserved EF (HFpEF). (sources: Inamdar *et al*., 2016; Cleveland Clinic).

Figure 15: Overview of heart failure



Source: First Berlin Equity Research, Cardiol Therapeutics Inc

Incidence and diagnosis HF is typically a disease of the elderly population (>60 years) and is reported to affect about 2–3% of people in the US. According to the Centers for Disease Control and Prevention, ~6.2m Americans have HF, and 380k died from HF in 2018. More than 870k people are diagnosed with HF each year. In 2013, the HF direct costs were ~USD32bn, they included costs for health care services, medicines to treat heart failure, and missed days of work; these costs are projected to increase by about three-fold by 2030. In 2011, the estimated lifetime cost of HF per individual patient was USD 110k/year, with more than three-fourths of this cost consumed by in-hospital care (sources: Inamdar *et al.*, 2016.

Diagnosing HF is similar to pericarditis and myocarditis, including blood tests, ECG and imaging tests such as X-ray, echocardiogram, cardiac CT and MRI (sources: Inamdar *et al*., 2016; Mayo Clinic).

Treatment of HF – DHF is a disease with poor treatment outcome Standard treatment in HF is chiefly cardiac medications to help control its symptoms, including the hypertension and reversing or slowing the cardiac and peripheral dysfunction. This includes the administration of beta blockers, ACE inhibitors, angiotensin II receptor blockers, diuretics, etc. Patients with systolic HF usually respond favourably to standard therapies and demonstrate a better prognosis. In contrast, patients with diastolic HF typically do not respond to standard therapies (except for beta blockers and SGLT-2 Inhibitors), and have poor prognosis care (sources: Inamdar *et al*., 2016; Mayo Clinic).

Overall HF market will continue to grow at a double-digit percentage rate The global pharmaceutical HF drugs market is expected to grow at a CAGR of 14.6% from USD 6.2bn in 2021 to USD 20.2bn in 2030. The main growth drivers include an ageing population, longer life expectancy, the rising prevalence of HF-associated co-morbidities (e.g. obesity, diabetes, hypertension), and new product launches. The ACE-inhibitors segment dominated the market in 2021 with a revenue share of over 30%; the US represents >76% of the world HF market (source: Grand View Research, 2021).

PRECLINICAL DEVELOPMENT OF A SUBCUTANEOUS FORMULATION OF CANNABIDIOL

The new formulation is still in preclinical stage – we believe the company will still require up to two years to have it ready to enter clinical development Cardiol is developing a novel subcutaneously administered formulation of cannabidiol targeting the inflammation and fibrosis typically associated with DHF. This formulation intends to improve cannabidiol's bioavailability in the blood compared to the current oral formulation, enabling this way that more cannabidiol reaches the heart. The main challenge for the company is having a cannabidiol formulation with aqueous properties, which represents a substantial change from the natural cannabidiol's oily characteristics. At the present preclinical development stage, we estimate the company may still need about two years to have a final formulation ready. Not to forget that substantial company resources will focus on the development of the two lead pericarditis and myocarditis indications.

Preclinical evidence supports cannabidiol's positive effect on DHF's underlying inflammation and fibrosis Two main *in vitro* studies, the one conducted by an independent research group and the other by a Cardiol's partner network research group, support the large potential of cannabidiol in DHF. The two *in vitro* studies investigated HF models and concluded that cannabidiol shows a cardioprotective effect in HF, it attenuates inflammation, and reduces and also promotes the reversal of mechanisms that play a role in HF fibrosis. The two studies were:

- "Cardioprotective effect of cannabidiol in a non-ischemic model of heart failure"; Lozano *et al*., 2020;
- "Cannabidiol inhibits and also promotes reversal of mechanisms leading to cardiac fibrosis"; Krishnamoorthi *et al*., 2022.

FINANCIAL HISTORY AND OUTLOOK

Cardiol's financial statements are prepared in accordance with the International Financial Reporting Standards (IFRS).

FINANCIAL HISTORY

Income statement 2022 – The LANCER study plus preparation for the international phase II acute myocarditis (AM) trial were the main cost drivers Cardiol's financial statement is typical of a development-stage biotech company. The firm is generating no drug-related revenues and is loss-making.

There are two relevant pieces of historical information to consider when looking at the OPEX and EBIT figures summarised in table 9. (1) Cardiol received in September 2020 the FDA's NDA clearance to conduct CardiolRx™'s largest-ever international phase II/III LANCER clinical trial in 422 patients with COVID-19 and cardiac inflammation. The company appointed a contract research organisation (CRO) in December, and this study took place between April 2021 and October 2022 when it was cancelled due to insufficient patients/appearance of events. Also, the international phase II ARCHER study with 100 AM patients started in August 2022, significantly impacting R&D expenses. Mainly due to these two large trials, R&D expenses increased by CAD 8.1m to CAD 19.0m in 2022 (2021: CAD 10.9m). (2) The 2021 listing on Nasdaq and increased financing initiatives led to high general & administrative costs associated with corporate communications and investor relations. These measures, coupled with lower G&A costs in connection with the LANCER study in 2022, were the main reasons for the CAD 5.5m decline in general & administrative expenses to CAD 22.4m in 2022 (2021: CAD 27.9m). The EBIT loss widened to CAD -41.3m (2021: CAD -38.7m).

The net financial result grew to CAD 4.0m, thanks to a foreign exchange gain of CAD 2.8m (2021: CAD 1.9m) and a higher net interest result of CAD 1.2m (2021: CAD 106k) traced to a revaluation of funds held in USD. The company booked non-cash, non-operating income of CAD 6.4m (2021: CAD 5.0m) stemming from a change in value of the derivative liability of CAD 6.2m (2021: CAD 4.9m) in connection with warrants issued on 5 November 2021 as part of a financing measure (see point 3 in the balance sheet analysis overleaf), and other income of CAD 164k (2021: CAD 112k) from tax credits. Cardiol reported a net loss of CAD -30.9m (2021: CAD -31.6m), which equates to CAD -0.49 p/s (2021: CAD -0.73 p/s).

Table 9: Income statement 2022 vs 2021 (selected items)

in CAD'000	2022	2021	Delta
Revenue	**0**	**79**	**-**
General & Administrative	-22,374	-27,873	*-20%*
Research & Development	-18,962	-10,870	*74%*
OPEX	-41,336	-38,744	*7%*
EBIT	**-41,336**	**-38,664**	*7%*
Net financial result	4,000	1,998	*100%*
Non-operating income/expenses	6,406	5,029	*27%*
Net income	**-30,931**	**-31,638**	*-2%*

Source: Cardiol Therapeutics Inc

Balance sheet 2022 Cardiol's cash position declined to CAD 59.5m at YE 2022 (2021: CAD 83.9m) due to funding of ongoing operations. Based on the company's planned burn rate, management expect that the cash runway will reach into 2026. Similarly, Cardiol's equity position dropped to CAD 52.2m at YE 2022 (2021: CAD 76.2m), corresponding to an equity ratio (ER) of 84% (2021 ER: 87%). The three further most noteworthy positions on the balance sheet were:

1) Other current assets (prepaid expenses) in connection with R&D and clinical trials: declined to CAD 1.5m at YE 2022 (2021:CAD 2.8m) chiefly due to progress achieved in the prepaid programmes;
2) Accounts payables/accrued liabilities: increased from CAD 4.9m in 2021 to CAD 9.3m by YE 2022 and are also chiefly related to R&D and clinical trials expenses;
3) Derivative liabilities (non-cash): were valued at CAD 6.7m in 2021 and declined to CAD 0.4m at YE 2022. The lower value of the liabilities is chiefly due to Cardiol's sharp share price decline from USD 2.55 on 5 November 2021 when the 8.2m warrants were issued to USD 0.51 at YE 2022. The warrants are exercisable at the price of USD 3.75 p/s within three years and are currently out of the money.

Table 10: Balance sheet 2022 vs 2021 (selected items)

in CAD'000	2022	2021	Delta
Cash and cash equivalents	59,470	83,899	*-29%*
Accounts receivables	480	407	*18%*
Other current assets	1,488	2,834	*-48%*
Current Assets, Total	**61,438**	**87,140**	*-29%*
Property plant and equipment	296	356	*-17%*
Intangible assets	295	379	*-22%*
Non-Current Assets, Total	**591**	**736**	*-20%*
Accounts payable	9,334	4,859	*92%*
Other current liabilities	50	45	*13%*
Derivative liabilities	420	6,661	*-94%*
Other LT liabilites	22	73	*-69%*
Total Liabilities	**9,827**	**11,638**	*-16%*
Equity	52,202	76,238	*-32%*
Equity ratio	84%	87%	-

Source: Cardiol Therapeutics Inc

Cash flow statement 2022 In 2022, negative cash flow from operating activities increased to CAD -27.2m (2021: CAD -23.5m). The increase is chiefly related to higher operating expenses in connection with R&D. CAPEX plays a minor role at Cardiol, rising to CAD 75k in 2022 from CAD 13k in 2021. In 2022, cash flow from financing activities declined to CAD -54k stemming from lease payments. In 2021 cash flow from financing amounted to CAD 93.4m due to fundraising activity through equity and warrants placement and exercise of stock options. These financing measures provide Cardiol with a comfortable cash runway into 2026. Thus, net cash flow in 2022 came in at CAD -27.3m (2021: CAD 69.9m).

Table 11: Cash flow statement 2022 vs 2021 (selected items)

in CAD'000	2022	2021	Delta
Operating cash flow	-27,220	-23,540	*16%*
Cash flow from investing	-75	-13	*478%*
Cash flow from financing	-54	93,438	-
Net cash flow	-27,349	69,885	-

Source: Cardiol Therapeutics Inc

FINANCIAL OUTLOOK

Income statement Given that Cardiol's lead oral drug candidate CardiolRx™ entered phase II development in two indications, we anticipate first revenues from its potential market launch in the recurrent pericarditis indication by 2026. We have assumed the potential market launch in the second indication of acute myocarditis by 2028.

Considering that the large international LANCER study was terminated in 2022, we have forecast OPEX of CAD 27.0m in 2023, well below the previous year's peak of CAD 41.3m. We forecast a positive net financial result of CAD 0.5m. We thus expect a net loss of CAD 26.5m in 2023. Going forward, we project OPEX to decline to CAD 24m in 2024 and CAD 19m in 2025. The two ongoing phase II studies in AM and RP have a smaller scope and patient size than LANCER. Our scenario includes expenses for both phase II trials, a phase III study in RP, and ongoing R&D for the subcutaneous formulation in heart failure. We project that a pharmaceutical partner will finance the expensive phase III study in AM and give an overview of our financial projections in table 12 below.

Table 12: Income Statement KPIs 2020-2025E

in CAD'000	2020	2021	2022	2023E	2024E	2025E
Revenue	0	79	0	0	0	0
General & Administrative	-10,088	-27,873	-22,374	-16,000	-14,000	-11,000
Research & Development	-10,603	-10,870	-18,962	-11,000	-10,000	-8,000
OPEX	-20,690	-38,744	-41,336	-27,000	-24,000	-19,000
EBIT	**-20,690**	**-38,664**	**-41,336**	**-27,000**	**-24,000**	**-19,000**
Net financial result	42	1,998	4,000	500	300	100
Non-operating income/expenses	7	5,029	6,406	0	0	0
Net income	**-20,641**	**-31,638**	**-30,931**	**-26,500**	**-23,700**	**-18,900**

Source: First Berlin Equity Research, Cardiol Therapeutics Inc

Balance sheet We estimate the company will progressively spend cash in the clinical development of its two lead RP and AM indications and its operations in the period 2023-2025 (see table 13). We therefore project that the cash position will decline from CAD 59.5 at YE 2022 to CAD 14.5m in 2025. As Cardiol has done in the past, we have assumed that it will continue financing some of its expenses with stock payments. Also, considering that cash may reach until approximately 2026, we look for Cardiol to raise capital of CAD 10.0m in 2025 to further extend their cash runway. With these capital measures, the company will be capable of adequately funding operations until the business model of Cardiol becomes self-sustaining by 2027 (assuming a successful launch of CardiolRx™ in RP in H2 2026). At that point, the company will generate enough cash to finance further organic growth. This will be reflected in a progressively growing cash position from 2026.

Table 13: Balance sheet KPIs 2020-2025E

in CAD'000	2020	2021	2022	2023E	2024E	2025E
Cash and cash equivalents	14,025	83,899	59,470	39,736	19,948	14,518
Accounts receivables	220	407	480	460	450	420
Other current assets	705	2,834	1,488	908	817	653
Current Assets, Total	**14,950**	**87,140**	**61,438**	**41,103**	**21,214**	**15,591**
Property plant and equipment	479	356	296	227	185	179
Intangible assets	464	379	295	210	126	41
Non-Current Assets, Total	**943**	**736**	**591**	**437**	**311**	**220**
Accounts payable	2,466	4,859	9,334	8,401	7,561	6,805
Other current liabilities	52	45	50	52	55	57
Derivative liabilities	0	6,661	420	420	0	0
Other LT liabilites	105	73	22	18	14	11
Total Liabilities	**2,623**	**11,638**	**9,827**	**8,891**	**7,630**	**6,873**
Equity	13,270	76,238	52,202	32,650	13,896	8,939
Equity ratio	83%	87%	84%	79%	65%	57%

Source: First Berlin Equity Research, Cardiol Therapeutics Inc

Cash flow statement We expect further drug development activity but with smaller trials than the phase II/III LANCER study conducted in the previous two years to result in falling negative operating cash flows in the period 2023-2025. We forecast a negative operating cash flow of CAD -19.6m for 2023, declining to CAD -15.3m for 2025. We expect Cardiol to continue outsourcing to Clinical Research Organisations (CROs) the clinical development of its lead programmes and therefore see minimal CAPEX investment in the forecasting period. We do not expect any significant financing measures (i.e. financial cash flow) in the period 2023-2024. In 2025 we have assumed a CAD 10m capital increase. We anticipate net cash flow to total CAD -19.7m in 2023 and provide an overview of our cash flow projections in table 14 below. Going forward, we estimate that a potential approval and commercialisation of CardiolRx™ in RP in 2026 will drive a strengthening of operating performance, having a positive impact on the company's free cash flow and net cash flow.

Table 14: Cash flow statement KPIs 2020-2025E

in CAD'000	2020	2021	2022	2023E	2024E	2025E
Operating cash flow	-9,129	-23,540	-27,220	-19,618	-19,650	-15,260
Cash flow from investing	-41	-13	-75	-60	-80	-110
Cash flow from financing	16,295	93,438	-54	-56	-58	9,940
Net cash flow	7,125	69,885	-27,349	-19,734	-19,788	-5,430

Source: First Berlin Equity Research, Cardiol Therapeutics Inc

NEWSFLOW

In our view, Cardiol's stock price will be driven by news about its pipeline as well as by the achievement of financial milestones. We expect the company to make a number of announcements during the coming 12 months which will act as catalysts for the stock. These include:

Pipeline

- Headline results of CardiolRx™'s US pilot phase II study in 25 RP patients planned for early 2024.

Financial results

The company publishes financial results and a "Management's Discussion and Analysis" (MDA) report on a quarterly basis. We expect the publication of financial results, including detailed updates on the business development and the R&D pipeline, as follows:

- Q1 2023 results and MDA report are due on 15 May 2023.
- Q2 2023 results and MDA report are due on 14 August 2023.
- Q3 2023 results and MDA report are due on 14 November 2023.

SHAREHOLDERS & STOCK INFORMATION

Stock Information	
ISIN	CA14161Y2006
WKN	A2PA9E
Bloomberg ticker	CRDL:US
No. of issued shares	64,097,536
Transparency Standard	Nasdaq
Country	Canada, US
Sector	Biotechnology
Subsector	Biotechnology

Source: Bloomberg, Nasdaq Stock Exchange, First Berlin Equity Research

Shareholder Structure	
MMCAP International Inc	5.2%
Management and Directors	4.4%
Advisorshares Investments LLC	1.7%
Mirae Asset Global Investments Co Ltd	1.7%
Freefloat & others	86.9%

Source: Nasdaq Stock Exchange, Cardiol Therapeutics Inc.

MANAGEMENT

MANAGEMENT BOARD

David Elsley, MBA, President and CEO

Mr Elsley is a serial entrepreneur with a proven track record of developing, financing and managing all aspects of corporate development in biotechnology and high-growth biotech organisations. He founded Cardiol Therapeutics Inc in 2017. In 1990, Mr. Elsley founded Vasogen Inc, a biotechnology company focused on the research and commercial development of novel therapeutics for the treatment of heart failure and other inflammatory conditions. Mr Elsley assembled a team of management, directors and scientific advisors comprising industry professionals and thought leaders from North America and Europe. Mr Elsley managed and directed Vasogen's growth from start-up to an organisation employing over 250 people with operations and R&D programs in Canada, the United States and Europe. He established the R&D infrastructure, partnerships, manufacturing capability, and corporate quality systems necessary to advance two anti-inflammatory therapies from concept to completion of international multi-centre pivotal phase III clinical trials involving 2,500 patients. Vasogen went public on the TSX and the Nasdaq, raising over USD 200m to support corporate development and reached a market capitalisation of >USD 1bn. Mr Elsley holds a Master of Business Administration from the Richard Ivey School of Business, University of Western Ontario.

Chris Waddick, MBA/CPA/CMA, CFO

Mr Waddick has >30 years experience in financial and executive roles in the biotechnology and energy industries, with substantial knowledge of public company management and corporate governance, and in designing, building, and managing financial processes and infrastructure. Mr Waddick has served as CFO and Corporate Secretary of Cardiol since 16 August 2018. He also serves as Executive Vice President and CFO for the private Ontario energy company Active Business Services where he was retained by the shareholders to refinance the company and establish a new strategic direction. Mr Waddick worked for >12 years at Vasogen Inc, the heart failures biotech company founded by Mr Elsley. While serving as CFO and COO, the company grew from start-up to an organisation employing >250 employees and went public on the TSX and the NASDAQ, raising > USD 200m and reaching a market capitalisation of >USD 1bn. Prior to Vasogen, he held progressively senior financial positions at Magna International Inc. and Union Gas Limited. Mr Waddick is a CPA and earned a business degree from Wilfrid Laurier University and a Master of Business Administration from York University.

Andrew Hamer, MBChB, Chief Medical Officer and Head of R&D

Dr Hamer brings 30 years of experience in the global life science industry, medical affairs, and cardiology practice. Most recently he served as Executive Director, Global Development-Cardiometabolic at California-based Amgen Inc, where he led the Global Development group for Repatha®, the LDL cholesterol lowering PCSK9-inhibitor evolocumab, which generated revenues of almost USD 900m in 2020. As development lead, Dr Hamer headed the Repatha® global evidence generation team collaborating with safety, regulatory, health economics, observational research, scientific communications, publications, medical affairs, and clinical operations teams to design and execute several multi-centre clinical trials to support FDA and international regulatory filings. Prior to his five-year tenure with Amgen, Dr Hamer served for two years as VP Medical Affairs at Capricor Therapeutics Inc, where he was responsible for the development of novel therapeutics for heart disease and for the supervision of the clinical operations of the company, including clinical trial design and execution. Prior to his life science career, Dr Hamer practiced cardiology and internal medicine in New Zealand for 19 years. He was also Chief Cardiologist at Nelson Hospital, Nelson Marlborough District Health Board, while

concurrently leading cardiac services nationally in New Zealand. Dr Hamer graduated with a medical degree (MBChB) from the University of Otago, New Zealand. His clinical research training took place at various centres in New Zealand and London, UK, followed by a cardiology fellowship at Deaconess Hospital, Harvard Medical School, Boston. Dr Hamer has co-authored many high-quality peer-reviewed scientific publications reflecting his considerable experience as a clinical trialist, having served as a principal or co-investigator for 40 multi-centre clinical trials in therapies for acute coronary syndrome, heart failure, hypertension, cholesterol disorders, atrial fibrillation, and diabetes.

Bernard Lim, MIET, CEng (UK), COO

Mr Lim has a proven track record of >30 years as a senior executive leading life science companies including biotechnology, diagnostics, medical devices, and high-technology companies in North America and Europe. He leads senior management teams through a sustained focus on strategy, rapid scale up and increasing talent depth to expand markets served. He was founder and CEO of a highly successful drug delivery company that he led from R&D through to commercialisation and its eventual acquisition by Eli Lily. As Chair of the Board of Acuity Insights, he guided its spinout from the university and its subsequent growth to become market leader in the US and Canada. In addition, as Chair of the Board and CEO of AndersDx (UK), he led its turnaround and growth. He is also currently Chair of the Board of Front Line Medical Technologies, a vascular trauma company. Mr Lim was Board Director of Aventamed (Ireland) recently acquired by Karl Storz, Senior Vice President, Operations for Vasogen, as well as head of UK operations for a technology multinational where he scaled its operations exponentially and delivered multifold improvements in quality and financial performance. He was CEO of a glaucoma, Alzheimer's and IVD company and prior to that head of R&D for a global neonatology and paediatrics company. Over his career, he has delivered exceptional results in fast growing companies and held corporate roles focused on increasing innovation while accelerating and sustaining growth. In addition to his corporate roles, he serves as an external independent expert reviewer on public sector life science investment programs.

BOARD OF DIRECTORS

Guillermo Torre-Amione, MD, PhD, Chairman

Dr Torre-Amione Board is certified in cardiovascular disease and Advanced Heart Failure/Transplant Cardiology. He is former chief of the Heart Failure Division and former medical director of Cardiac Transplantation at the Houston Methodist DeBakey Heart & Vascular Centre. He is also Professor of Cardiology at the Methodist Hospital Research Institute, Houston, Professor of Medicine at the Weill Cornell Medical College of Cornell University, New York, and President of TecSalud, an academic medical centre and medical school of the Instituto Tecnológico y de Estudios Superiores de Monterrey (ITESM) in Mexico. Dr Torre-Amione spearheads the Gene and Judy Campbell Laboratory for Cardiac Transplant Research, where his primary areas of research include heart failure, cardiac transplant, and the role of the immune response in modulating the progression of heart failure. Dr Torre-Amione conducted a series of clinical studies that led to an FDA-approved Phase II clinical trial of neurostimulation in heart failure, a novel approach to the treatment of patients with advanced heart failure. Other relevant clinical investigations include a study with cardiac transplant patients designed to impact the cardiac hypertrophy that naturally follows transplantation, a protocol for autologous stem cell transfer in patients with advanced refractory heart failure, and a novel study involving plasma exchange in advanced heart failure patients. After receiving his medical degree from the ITESM in Monterrey, Mexico, Dr Torre-Amione moved to Chicago, where he conducted graduate studies in immunology that led to a doctorate degree in immunology from the University of Chicago. He then moved to Houston to complete his internship, residency, and cardiology fellowship at Baylor College of Medicine, where he received his first academic appointment as a clinical instructor in 1995.

Dr. Torre-Amione has published more than 170 manuscripts in peer-reviewed journals and currently divides his time between his clinical and academic activities at the Methodist Hospital in Houston and at ITESM in Monterrey, Mexico.

Jennifer M. Chao, BA, Director

Ms Chao has over 25 years of experience in the biotech and life sciences industries focused primarily on finance and corporate strategy. She is Managing Partner of CoreStrategies Management, LLC, a company she founded in 2008 to provide transformational corporate and financial strategies to biotech/life science companies for maximising core valuation. She also serves as a biopharma securities expert witness for high-level biopharma litigation matters, working with large economic consulting firms and law firms; cases have involved material and fair disclosure, valuation, and insider trading. She currently serves on the board of directors of Endo Pharmaceuticals and is a member of the Audit Committee and Compliance Committee. Ms Chao also serves on the board of directors of Edesa Biotech as Chair of Nominating and Corporate Governance, and a member of the Audit Committee. Prior to joining Endo, Ms Chao served as Chairman of the Board of BioSpecifics Technologies Corp (BioSpecifics) from October 2019 until its acquisition by Endo for approximately US 660m in December 2020. She also served as Chair of BioSpecifics' Compensation Committee and as a member of the Audit Committee, Strategy Committee, Intellectual Property Committee, and Nominating and Corporate Governance Committee from 2015 to 2020. Additionally, from 2004 to 2008, Ms Chao was Managing Director and Senior Lead Biotechnology Securities Analyst at Deutsche Bank, responsible for US large- and small- to mid-cap biotechnology companies with global client coverage; and was known for differentiated fundamentals securities analysis and high visibility coverage of game changing technologies, paradigm shifting treatment algorithms, industry trends and portfolio risk/reward management. Prior to that, she served as Managing Director and Senior Lead Biotechnology Analyst at RBC Capital Markets and VP, Senior Biotechnology Analyst at Leerink Swann & Co. Ms Chao was a research fellow at Massachusetts General Hospital/Harvard Medical School, as a recipient of the BioMedical Research Career Award, and received her BA in Politics and Greek Classics from New York University.

Teri Loxam, MBA, Director

Ms Loxam has over 25 years of experience in pharmaceutical, life sciences and the entertainment industries with diverse roles spanning strategy, investor relations, finance and communications. Ms Loxam joined Kira Pharmaceuticals in November 2021 as COO and CFO. In this role, she oversees finance, operations, and strategic functions for the company. Prior to joining Kira, Ms Loxam served as SQZ Biotech's CFO where she led the company's financial operations, investor relations and communications/public relations functions. While at SQZ, she was instrumental in helping the company raise over USD 200m in private and public funding, including taking the company public through an IPO on the NYSE in October 2020. Before that, Ms Loxam served as Sr Vice President of Investor Relations and Global Communications at Merck. In this role, she led its investor relations and investment community interactions as well as its internal and external communications efforts globally. Prior to Merck, she was Vice President, Investor Relations for IMAX Corporation, where she reshaped the entertainment company's investor strategy, helping to convert its investor base and go public in China with an IPO on the Hong Kong Exchange. Ms Loxam also spent over a decade at Bristol-Myers Squibb in a variety of roles of increasing responsibility across Strategy, Treasury and Investor Relations. She started her career as a marine biologist and worked at Sea World of San Diego before making a transition into business. Ms Loxam is a member of the board of directors of Vaxcyte Inc. She holds an MBA from the University of California, Irvine, and a Bachelor of Science degree in Biology from the University of Victoria, BC, Canada.

Peter Pekos , BSc, MSc, Director

Mr Pekos, is a veteran of the pharmaceutical services industry. He co-founded Dalton Pharma Services (Dalton) in 1986. Over a period of 36 years, he directed as CEO Dalton's growth based on strong client relationships throughout the major global economies, including the world's largest pharmaceutical companies. Dalton provides pharma and biotech clients with an array of integrated contract development and cGMP manufacturing services in a world-class 42k square foot facility, with more than 140 employees, in the heart of one of Canada's largest biomedical clusters. In 1983, he obtained a Chemistry/Biochemistry Double Specialist Degree with a Minor in Biology from the University of Toronto. In 1986, he completed a Master's Degree in synthetic chemistry at York University, and with his Professor, Doug Butler, founded Dalton with a very modest amount of capital. Mr Pekos also founded Ashbury Biologicals Inc, a phyto-pharmaceutical company, Jupiter Consumer Products, a company that targeted the development of adult-focused confections, and several other technology-based companies focused on advanced materials and pharmaceutical development tools. Mr Pekos was founding Chairman of ventureLAB a Regional Innovation Centre located at IBM's York Region campus. VentureLAB guides government program delivery to support the innovation ecosystem for biotechnology and related industries in southern Ontario.

Colin G. Stott, BSc (Hons), Director

Mr Stott is a veteran of the pharmaceutical and biotech industries having almost 30 years' experience in preclinical and clinical development with specific expertise in the development of cannabinoid-based medicines and 19 years' experience in the field. Currently COO of Alterola Biotech Inc, Mr Stott is the former Scientific Affairs Director, International and R&D Operations Director for GW Pharmaceuticals plc ("GW Pharma"), a world leader in the development of cannabinoid therapeutics. As R&D Operations Director at GW Pharma for over 16 years, he was a key player in the development of their discovery and development pipeline, and was closely involved in the Marketing Authorization Application submission and approval of Sativex® and the New Drug Application submission of Epidiolex®, which was approved by the US Food and Drug Administration as an orphan drug for the treatment of rare forms of paediatric epilepsy in June 2018. More recently, as Scientific Affairs Director, International, he was part of the Medical Affairs team responsible for the preparation of the international launch of Epidiolex®. Prior to his 19-year tenure at GW Pharmaceuticals, Mr Stott held various roles in clinical R&D across a range of therapeutic areas, including: cardiology, oncology, urology, dermatology, metabolic disorders, neurology, haematology, and organ transplantation. Mr Stott holds a BSc (Hons) in Medicinal & Pharmaceutical Chemistry and a Diploma in Industrial Studies from Loughborough University of Technology, UK, as well as a Post Graduate Diploma in Clinical Research from the Welsh School of Pharmacy, Cardiff University, UK. He has published over 20 research papers and is a named inventor on 17 international patent applications.

Michael J Willner, Esq, Director

Mr Willner has practiced as both an Attorney and a Certified Public Accountant. He graduated from Emory University Law School as a member of the Emory Law Review. Subsequently, he practiced real estate and corporate law with New York City-based Milbank, Tweed, Hadley & McCloy, one of the nation's most prominent international law firms. Prior to his legal career, Mr Willner was employed by the former national accounting firm Arthur Andersen & Company, where he practiced in the tax department. Mr Willner has been a very active and successful opportunistic investor for over forty years. He is the founder of Willner Capital Inc, an investment company specialising in public and private equity, as well as debt instruments. Over the past ten years, Willner Capital has made significant investments in both the biotechnology and pharmaceutical cannabinoid industries, focusing primarily on clinical-stage companies that seek to address significant unmet medical needs. Mr Willner has served as a moderator and participant on numerous panel discussions and advisory boards regarding his investments in the pharmaceutical and the cannabinoid industry.

INCOME STATEMENT

All figures in CAD '000	2020	2021	2022	2023E	2024E	2025E
Revenue	**0**	**79**	**0**	**0**	**0**	**0**
Cost of goods sold	0	0	0	0	0	0
Gross profit	0	79	0	0	0	0
General & Administrative	-10,088	-27,873	-22,374	-16,000	-14,000	-11,000
Research & Development	-10,603	-10,870	-18,962	-11,000	-10,000	-8,000
Total operating expenses (OPEX)	**-20,690**	**-38,744**	**-41,336**	**-27,000**	**-24,000**	**-19,000**
Operating income (EBIT)	**-20,690**	**-38,664**	**-41,336**	**-27,000**	**-24,000**	**-19,000**
Net financial result	42	1,998	4,000	500	300	100
Non-operating income/expenses	7	5,029	6,406	0	0	0
Pre-tax income (EBT)	**-20,641**	**-31,638**	**-30,931**	**-26,500**	**-23,700**	**-18,900**
Income taxes	0	0	0	0	0	0
Net income / loss	**-20,641**	**-31,638**	**-30,931**	**-26,500**	**-23,700**	**-18,900**
Diluted EPS (CAD)	**-0.69**	**-0.73**	**-0.49**	**-0.41**	**-0.34**	**-0.26**
Ratios						
EBIT Margin on Revenue	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
EBITDA Margin on Revenue	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Net Margin on Revenue	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Expenses as % of OPEX						
Sales & Marketing	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
General & Administrative	48.8%	71.9%	54.1%	59.3%	58.3%	57.9%
Research & Development	51.2%	28.1%	45.9%	40.7%	41.7%	42.1%
Y-Y Growth						
Revenue	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Operating income	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Net income/ loss	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

BALANCE SHEET

All figures in CAD '000	2020	2021	2022	2023E	2024E	2025E
Assets						
Current Assets, Total	**14,950**	**87,140**	**61,438**	**41,103**	**21,214**	**15,591**
Cash and cash equivalents	14,025	83,899	59,470	39,736	19,948	14,518
Accounts receivables	220	407	480	460	450	420
Inventories	18	0	0	0	0	0
Other current assets	687	2,834	1,488	908	817	653
Non-Current Assets, Total	**943**	**736**	**591**	**437**	**311**	**220**
Property plant and equipment	479	356	296	227	185	179
Intangible assets	464	379	295	210	126	41
Total Assets	**15,893**	**87,876**	**62,029**	**41,541**	**21,525**	**15,812**
Shareholders' Equity & Debt						
Current Liabilities, Total	**2,518**	**11,565**	**9,805**	**8,873**	**7,615**	**6,861**
Accounts payable	2,466	4,859	9,334	8,401	7,561	6,805
Derivative liabilities	0	6,661	420	420	0	0
Other current liabilities	52	45	50	52	55	57
Longterm Liabilities, Total	**105**	**73**	**22**	**18**	**14**	**11**
Other liabilities	105	73	22	18	14	11
Shareholders Equity	**13,270**	**76,238**	**52,202**	**32,650**	**13,896**	**8,939**
Total Consolidated Equity and Debt	**15,893**	**87,876**	**62,029**	**41,541**	**21,525**	**15,812**
Ratios						
Current ratio (x)	5.94	7.53	6.27	4.63	2.79	2.27
Quick ratio (x)	5.93	7.53	6.27	4.63	2.79	2.27
Net gearing	-105.7%	-110.0%	-113.9%	-121.7%	-143.6%	-162.4%
Book value per share (€)	0.44	1.76	0.84	0.50	0.20	0.12
Net debt	-14,025	-83,899	-59,470	-39,736	-19,948	-14,518
Equity ratio	83.5%	86.8%	84.2%	78.6%	64.6%	56.5%

CASH FLOW STATEMENT

All figures in CAD '000	2020	2021	2022	2023E	2024E	2025E
Net income	**-20,641**	**-31,638**	**-30,931**	**-26,500**	**-23,700**	**-18,900**
Interest, net	-42	-1,998	-4,000	-500	-300	-100
Tax provision	0	0	0	0	0	0
Non-operating items	-7	-5,029	-6,406	0	0	0
EBIT	**-20,690**	**-38,664**	**-41,336**	**-27,000**	**-24,000**	**-19,000**
Depreciation and amortisation	230	220	220	213	207	201
EBITDA	**-20,461**	**-38,444**	**-41,116**	**-26,787**	**-23,793**	**-18,799**
Derivative liability	0	-4,916	-6,241	0	-420	0
Share & warrant based payments	2,910	12,694	6,894	5,000	4,000	3,000
Changes in working capital	8,316	77	5,748	-331	-737	-561
Cash interest net	42	1,998	4,000	500	300	100
Other adjustments	63	5,052	3,495	2,000	1,000	1,000
Operating cash flow	**-9,129**	**-23,540**	**-27,220**	**-19,618**	**-19,650**	**-15,260**
CapEx	-41	-13	-75	-60	-80	-110
Free cash flow	**-9,170**	**-23,553**	**-27,295**	**-19,678**	**-19,730**	**-15,370**
Other investments	0	0	0	0	0	0
Cash flow from investing	**-41**	**-13**	**-75**	**-60**	**-80**	**-110**
Debt Financing, net	0	0	0	0	0	0
Equity Financing, net	16,345	93,489	0	0	0	10,000
Other financiing activities	-50	2,785	-54	-56	-58	-60
Cash flow from financing	**16,295**	**93,438**	**-54**	**-56**	**-58**	**9,940**
Net cash flows	**7,125**	**69,885**	**-27,349**	**-19,734**	**-19,788**	**-5,430**
Cash, start of the year	6,956	14,025	83,899	59,470	39,736	19,948
Impact of exchange rates on cash	-56	-11	2,920	0	0	0
Cash, end of the year	**14,025**	**83,899**	**59,470**	**39,736**	**19,948**	**14,518**

Y-Y Growth						
Operating Cashflow	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Free cashflow	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

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Category		1	2
Current market capitalisation (in €)		0 - 2 billion	> 2 billion
Strong Buy[1]	An expected favourable price trend of:	> 50%	> 30%
Buy	An expected favourable price trend of:	> 25%	> 15%
Add	An expected favourable price trend of:	0% to 25%	0% to 15%
Reduce	An expected negative price trend of:	0% to -15%	0% to -10%
Sell	An expected negative price trend of:	< -15%	< -10%

[1] The expected price trend is in combination with sizable confidence in the quality and forecast security of management.

Our recommendation system places each company into one of two market capitalisation categories. Category 1 companies have a market capitalisation of €0 – €2 billion, and Category 2 companies have a market capitalisation of > €2 billion. The expected return thresholds underlying our recommendation system are lower for Category 2 companies than for Category 1 companies. This reflects the generally lower level of risk associated with higher market capitalisation companies.

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Report No.:	Date of publication	Previous day closing price	Recommendation	Price target
Initial Report	Today	USD0.51	Buy	USD3.60

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