High Stakes and Heart Aches:

Why CBD Doesn't Work Against Inflammatory Heart Diseases

Cardiol Therapeutics (S): (TSX: CRDL) & (NASDAQ: CRDL)

Current Price: $1.89 CAD

PT: $0.19 cad (+90% return)

Thomas Giroux

December 2024

cad millions, ex per share

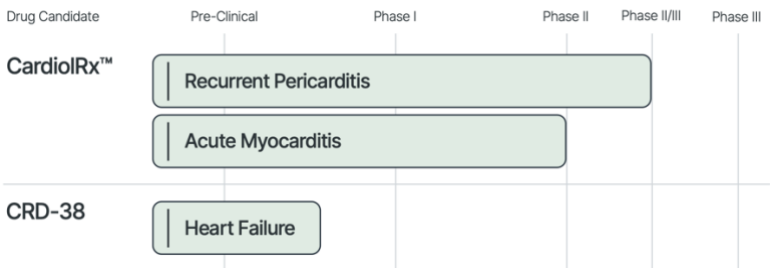
Price	$	1.89	20-Dec
Shares		81.6	Q324
MC		**154**	
Cash		16	Q324
Funded Debt		0.16	Q324
EV		**138**	
PIC		28	Q324
AD		(172)	Q324
Net Cash/Share	$	0.19	

Trading Stats:

Insider Ownership	3.91%	
Shares short	252.97K	20-Dec
Short % Out.	0.31%	

Description

Cardiol Therapeutics is a clinical stage biotech company headquartered in Oakville, Ontario and founded in 2017. The company is currently developing CardiolRx (stable oral cannabidiol) for recurrent pericarditis (RP) and acute myocarditis (AM), both indications are in phase II/III and phase II respectively. The firm is also developing CRD-38 (same CBD formulation, but subcutaneous administration) against heart failure (pre-clinical).



Recurrent Pericarditis and Acute Myocarditis

Recurrent pericarditis is the inflammation of the pericardium (external sac around the heart). For pericarditis to be considered recurrent, there needs to be recurrence after a period, without symptoms, of 4 to 6 weeks. We can measure the c-reactive proteins (CRP) as a clinical marker of inflammation (generally primary or secondary endpoint in trials). There are ~18,000 hospitalizations/year and 38,000/year cases in the US. The best treatment option is FDA-approved Rilonacept (KPL-914) which costs $270,000/year.

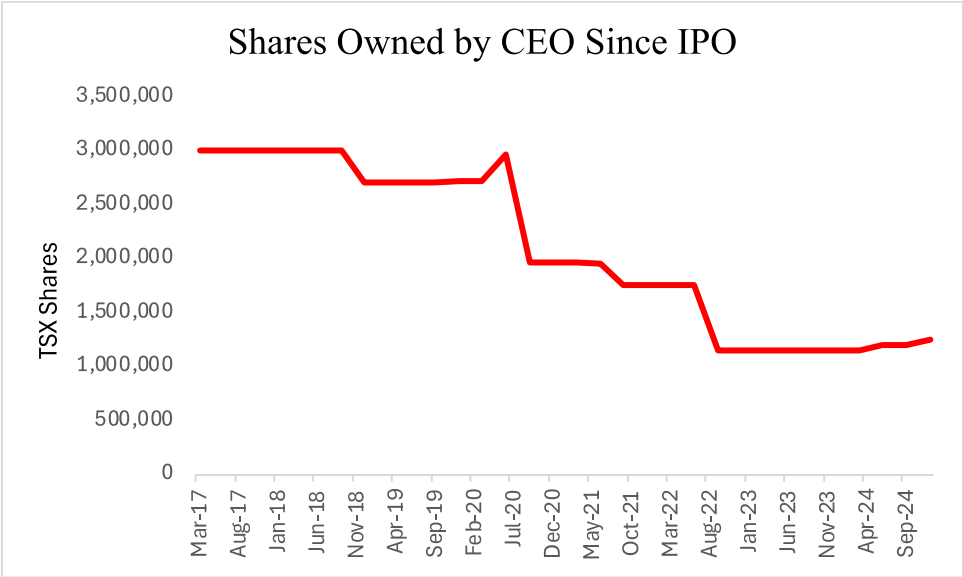
Acute myocarditis is the inflammation of the heart muscle (myocardium) from viral infections. There are 46,000/year cases of AM in the US with a mortality rate of 4-6% and 32,400 deaths/year worldwide (2019). There are no approved drugs for treating the disease.

The Interesting Bit – A Well-Timed IPO and Past Failures

The Canadian company incorporated on January 19, 2017, and IPO'd on December 20, 2018. All the while, the Canadian government legalized cannabis on October 17, 2018 (Bill C-45), thus fuelling market uproar in "weed stocks". I firmly believe that Cardiol simply timed its IPO very well to profit from the craze around Canadian cannabis stocks and allowed insiders to dump their equity during the euphoria, knowing that its lead drug didn't work (or match the efficacy of Rilonacept).

I believe Cardiol's Phase II/III and planned Phase III will fail and lead the firm to rapidly reassess its pipeline and find new targets, at a hefty price (or immense dilution via reverse-merger or equity offerings). My PT is $0.19 cad (net cash per share, as of Q3 '24). The timeline of these events are 2H of 2025 or early 2026.

What's more, David Elsley, the president and CEO of Cardiol has been in the biotech industry for almost 35 years and founded a company named Vasogen, in 1990. Cardiol's CFO, Chris Waddick has also served as CFO and COO of the company for 12 years. Curious enough, Vasogen targeted heart failure and inflammatory heart diseases (just like Cardiol), but ended reverse-merging with IntelliPharmceutics (IPC) in October 2009 due to inadequate liquidity to fund current projects. IPC went bankrupt in October 2024. The CEO has also been dumping his stake in Cardiol since IPO (-60%), even though he directly linked his confidence in Cardiol to his ownership in multiple past interviews.



CBD Description, Chemical Structure, PK and Receptors

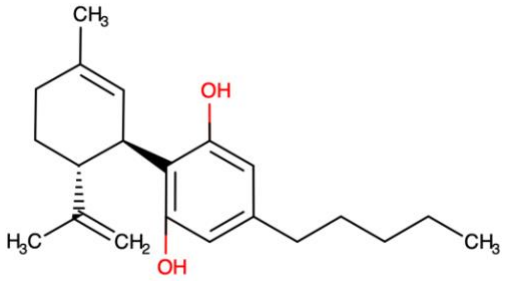
Cannabidiol (CBD) is a non-psychoactive chemical from the Sativa plant (marijuana), and although it resembles another chemical found in the plant (THC), it's not responsible for the "high" marijuana is known for. Instead, CBD interacts with systems responsible for inflammation control, nerve signaling and oxidative stress control.

CBD tends to move rapidly into fatty tissues like the heart, brain, liver and may spread to other areas of the body. It's broken down in the liver and excreted through waste. CBD's effects can vary depending on the delivery method (oral, inhaled and subcutaneously). It's generally safe with rare and mild side effects.

Cannabidiol also has great effects on pain perception (very important for thesis on Phase II results):

- CBD activates the TRPV1 receptors which are involved in sensing pain and inflammation, CBD can thus reduce the sensation of pain when activating TRPV1.
- CBD also acts as a modulator of GABAA receptors, which enhance the calming signals in the nervous system and reduces pain perception.
- CBD interacts with serotonin (5-HT1A) receptors responsible for mood and pain regulation. When CBD activates these receptors, it reduces pain and the emotional distress (stress, anxiety, etc.) associated with the latter.
- Cannabidiol also increases the levels of anandamide by inhibiting its breakdown. Anandamide interacts with CB1 receptors in the nervous system, thus reducing the intensity of pain signals.

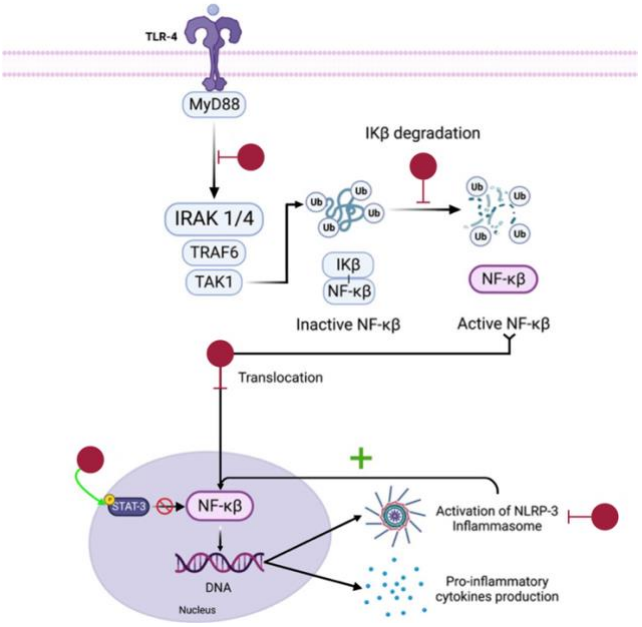
CBD has very low oral bioavailability at around 6% (most of the drug doesn't enter the bloodstream) and gets destroyed in the liver. The time to max concentration (Tmax) typically varies from 1 to 6 hours post-ingestion and has a half-life (stays in the body) for 18 to 32 hours.



Mechanism of Action (MOA) Simply Explained

Cannabidiol's MOA consists of inhibiting the NLRP3 inflammasome protein complex to prevent the creation of pro-inflammatory cytokines that lead to heart inflammation. This protein structure is essentially like an alarm system in your body and a part of the greater immune system. When you're combatting an infection, this "alarm system" (NLRP3) gets turned on and sometimes never turns off. This is the case because of the role NF-kβ plays in triggering NLRP3 and releasing cytokines that actively lead to inflammation. What CBD does is essentially switching off NF-kβ and prevents the release of cytokines (see picture below) and the functioning of NLRP3. The specific cytokines (IL-1 beta and alpha, IL-6) are the direct cause of the inflammation and once targeted, have been proved to stop/prevent recurrent pericarditis (Rilonacept with IL-1 target successfully proved its statistical significance in Rhapsody Phase III trial).

In sum, I do believe that Cardiol has chosen the correct target for Recurrent Pericarditis, I just don't believe CBD will prove to be a good drug against NLRP3, at least compared to Rilonacept.



The composition of CardiolRx is as follows (this includes the suppliers and manufacturers of synthetic CBD):

Ingredient	Function in formulation	Supplier / Catalog Number
(-)-cannabidiol (purified botanical)	Active Pharmaceutical Ingredient (API)	Dalton Pharma Services; CAS #13956-29-1
(-)-cannabidiol (synthetic)	Active Pharmaceutical Ingredient (API)	Noramco (now Purysis, Inc.); 75407; CAS #13956-29-1
(-)-cannabidiol (synthetic)	Active Pharmaceutical Ingredient (API)	Bio Vectra Inc.; Catalog Number 7082; Lot Number 49395; CAS #13956-29-1
β-caryophyllene (BCP) ≥80%, FC	Co-solvent and antioxidant	Sigma Aldrich; W225207; CAS # 87-44-5
Coconut Oil	Principal Solvent	Spectrum Chem.: C0110; CAS # 8001-31-8
MCT (C8, C10 triglycerides)	Principal Solvent	Vigon International, Inc. of Stroudsberg, Pennsylvania under product code 507177
Vitamin E (α-tocopherol, FCC) ≥95.5%	Antioxidant	Spectrum Chemicals; CAS # 10191-41-0

The CBD must be THC free and have at least 98% purity, the other components and proportions are detailed below:

INGREDIENT	AMOUNT (g)	AMOUNT (% w/v)
CBD	27	22.67
BCP	29.9	25.11
Coconut oil	61.2	51.41
Vitamin E	0.95	0.81

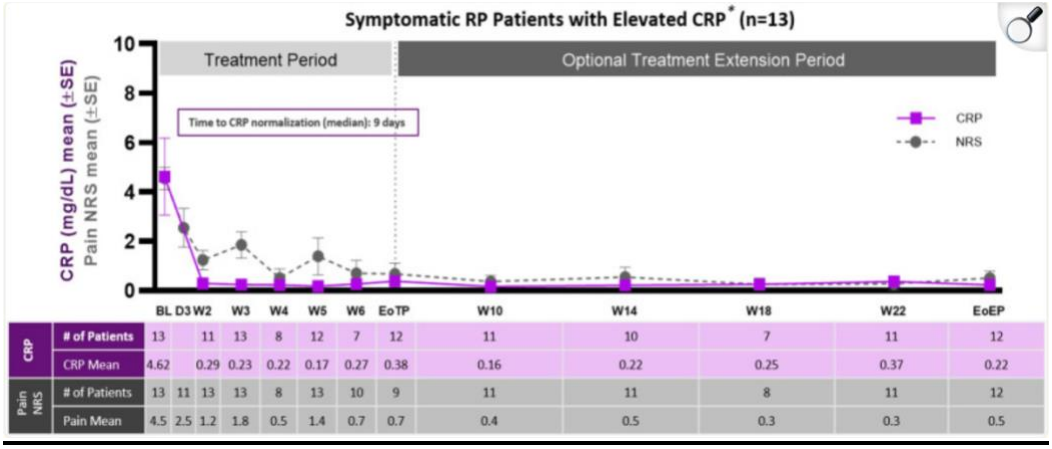
MAvERIC-Pilot Phase II Trial – Overview and Results Compared to Rilonacept:

The clinical trial was an open-label pilot study which enrolled 27 patients across 8 different sites in the US. The primary endpoint was the change in patient-reported pericarditis pain using a score from 0 to 10 (0 = no pain, 10 = worst pain), from baseline to 8 weeks.

What this means in plain English is that both the doctors administering the drug and the patients receiving it, knew they were getting the drug (instead of randomized placebo-controlled trials where neither hold any bias). The reason why this is so important is that according to Hawthorne's Effect, patients who know they're being studied tend to modify their behavior. In other words, since the patients are themselves evaluating their pain from 0 to 10, they can positively skew their results because they want/like to think they're receiving a beneficial treatment. The Numerical rating Score (NRS) is a less robust measurement of drug efficacy because it's prone to placebo-effect, open-label biases and individual pain tolerance.

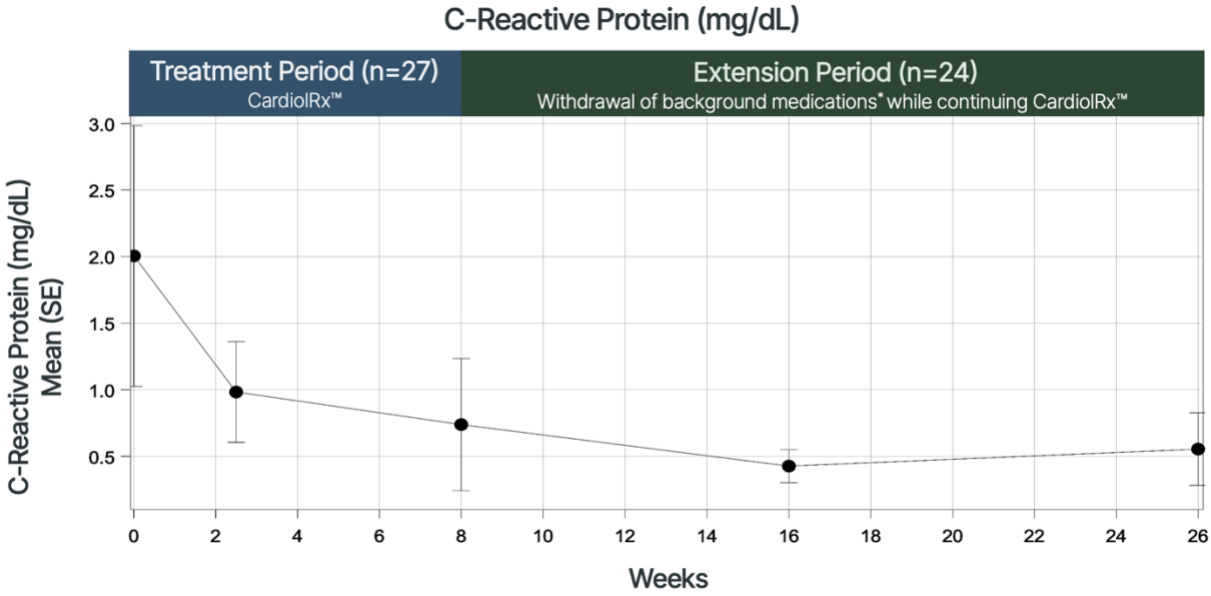
The more meaningful basis of evaluation should be the concentration of C-Reactive Proteins (CRP), because it leaves no room for patient manipulation. The lower the amount of CRP, the better. In the case of Rilonacept's Phase II, CRP decreased from 4.62 mg/dL at baseline to 0.38 mg/dL at the end of treatment (week 8) period and as low as 0.17 in week 5.

If you compare Rilonacept's Phase II trial (which Cardiol "copied" since the drug got approved) with Cardiol's, the difference in CRP concentration is greater for Rilonacept than for CBD at the end of the treatment period and extension period (look at third table). Normal levels of CRP are ≤ 0.3 mg/dL. Rilonacept reached this level at the end of the extension period, **CBD never did**.



		BL	D3	W2	W3	W4	W5	W6	EoTP	W10	W14	W18	W22	EoEP
CRP	# of Patients	13		11	13	8	12	7	12	11	10	7	11	12
	CRP Mean	4.62		0.29	0.23	0.22	0.17	0.27	0.38	0.16	0.22	0.25	0.37	0.22
Pain NRS	# of Patients	13	11	13	13	8	13	10	9	11	11	8	11	12
	Pain Mean	4.5	2.5	1.2	1.8	0.5	1.4	0.7	0.7	0.4	0.5	0.3	0.3	0.5

Rilonacept Phase II Results, Figure 2



Cardiol Corporate Presentation (Dec, '24), P.20

	CRP mean (mg/dL)				
	Baseline	Week 8 (End of TP)	Δ	Week 24 (Extension Period)	Δ
	n=13	*n=12*		*n=12*	
Rilonacept	4.62	0.38	**-91.8%**	0.22	**-95.2%**
	n=27	*n=27*		*n=24*	
CardiolRx	2	0.75	**-62.5%**	0.55	**-72.5%**

Even if we were to place emphasis on the NRS scores, Rilonacept still outperformed CBD at the end of both treatment and extension periods:

	NRS mean (pain from 0 to 10, 0 = no pain, 10 = worst pain)				
	Baseline	Week 8 (End of TP)	Δ	Week 24 (Extension Period)	Δ
	n=13	*n=9*		*n=12*	
Rilonacept	4.5	0.7	**-84.4%**	0.5	**-88.9%**
	n=27	*n=27*		*n=24*	
CardiolRx	5.8	2.1	**-63.8%**	1.6	**-72.4%**

In line with the pharmacokinetics detailed on p.3, it's very possible that CBD lowers NRS scores because of the role it plays with key pain-related receptors. CBD relieves pain in minutes to hours by activating TRPV1 (desensitizing pain receptors), enhancing GABAA (boosting calming signals), and stimulating 5-HT1A (reducing pain neurotransmitters). The anti-inflammatory effects the company claim (inhibiting NLRP3 inflammasome complex) take hours to days to materialize, because they involve slower gene expression and protein synthesis. This dual timeline explains why patients may feel quick pain relief from CBD while measurable reductions in inflammation take more time to manifest.

MOST IMPORTANTLY, time until pericarditis recurrence was also studied in both CBD and Rilonacept's Phase II trials and was used as primary endpoint in the Rilonacept Phase III trial. For Rilonacept's phase II, no recurrence in pericarditis were reported at n = 29 [10]. In CBD's phase II trial, 7/24 patients experienced a recurrence in pericarditis (~30% of patients) [2].

Phase II/III and Planned Phase III Trials Prediction - Comparison to Rilonacept

Rilonacept's Phase III (RHAPSODY) trial's primary endpoint aimed to measure the time until first pericarditis recurrence during withdrawal period. This means they measured how long it took for patients to experience recurrent pericarditis after randomly continuing Rilonacept or placebo.

The results for the Rilonacept group could not be calculated (according to Kiniksa) due to the low number of recurrent cases (most likely 0 or 1). This compares to the placebo group with a median time to recurrent pericarditis episode of 8.6 weeks (23 patients with recurrent episode out of 31 – or 74%) at $P<0.0001$ and Hazard Ratio of 0.04. This proves that Rilonacept is statistically significant in preventing recurrent pericarditis.

Cardiol is expected to start Phase II/III in Q4 '24 with 110 patients across 20 clinical sites. The study is a double-blind, placebo-controlled and multi-national trial to assess CardiolRx's impact on recurrent pericarditis. The primary endpoint is the number of patients free from recurrent pericarditis at 24 weeks. The secondary endpoint is the median time to a new episode of pericarditis recurrence. The changes in numerical rating score (NRS) and C-reactive protein levels (CRP) will also be recorded.

Because of underwhelming Phase II results, I DO NOT expect CBD to reach or beat Rilonacept in both the primary and secondary endpoints of the Phase II/III trial.

Summary

- CardiolRx (CBD) has a good target and very solid preclinical science with a strong safety profile
- The main indication to analyze is recurrent pericarditis, because if the company fails to get CBD to work against the RP, the odds of it working on acute myocarditis and heart failure are slim to none
- Both the CEO and CFO of Cardiol have had past mishaps in biotech with the same indications. Although past performance in the corporate world isn't indicative of future performance, when you juxtapose the very well-timed IPO (and active ingredient – CBD or weed) with the Canadian Gov's legalization of cannabis + overall sector craze at the time, the picture becomes dubious
- The CEO has been dumping shares since IPO, although he links his confidence to his stake
- No partnership, commercialization or option agreement to develop CBD (unlike Regeneron and Kiniksa agreement for Rilonacept and frequent industry practice)
- Underwhelming Phase II results in CRP and NRS scores VS Rilonacept. CRP levels never reached normalization at ≤ 0.3 mg/dL
- The NRS scores are akin to high subjectivity and might be falsely skewed because of CBD's innate analgesic effects on key pain receptors
- High number of Phase II recurrent cases (30% recurrent cases) VS Rilonacept (0% recurrent cases)

Risks and Caveats – Where I might be Wrong

- The drug isn't completely inefficient in terms of reducing cytokines concentration in *in vitro* pre-clinical tests [1, pages 10-11]
- The safety profile of the drug is very high and slightly better than Rilonacept's
- I expect the drug to be priced at ~20% of Rilonacept's $270,000/year usd (according to CEO, a month ago), which might positively tilt the FDA into approval
- Better administration (oral) versus Rilonacept's subcutneous admin

Bibliography

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4. Molecular and Cellular MOA of Cannabidiol
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7. Rilonacept (KLP-914) Phase II Trial Results
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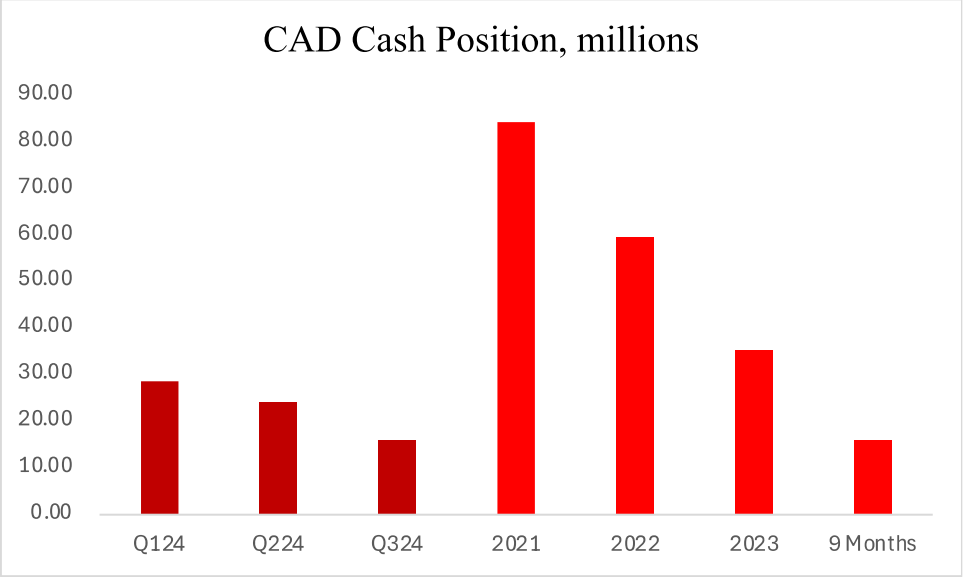
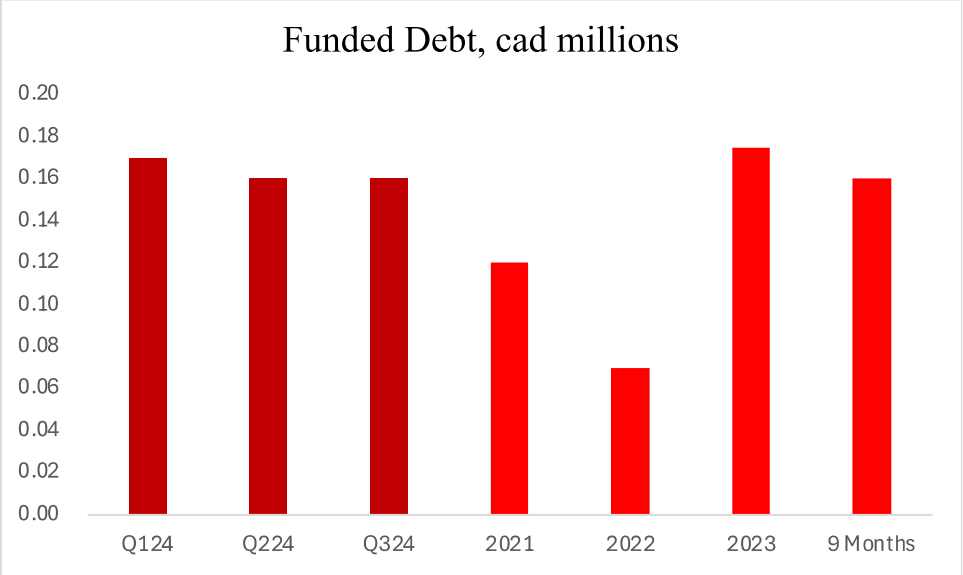
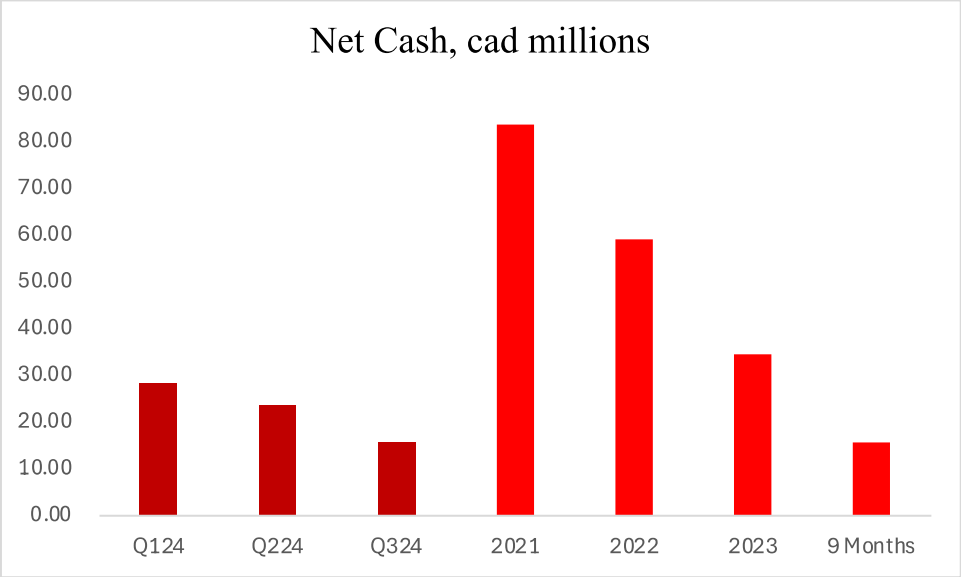
9. Cannabinoid Receptors and Their Relationship With Chronic Pain: A Narrative Review
10. Rilonacept's Phase II Trial Results
11. Rilonacept's Phase III Trial Results

Financial Data






Net Cash, cad millions
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
Q124
Q224
Q324
2021
2022
2023
9 Months

cad millions	Q124	Q224	Q324	2021	2022	2023	9 Months
Revenue	0.00	0.00	0.00	0.1	0.0	0.0	0.0
COGS	0.00	0.00	0.00	0.0	0.0	0.0	0.0
GP	0.00	0.00	0.00	0.1	0.0	0.0	0.0
R&D	3.32	2.71	3.75	10.9	19.0	14.2	9.8
SG&A	5.08	5.03	10.39	27.9	22.4	15.6	20.5
Operating Expenses	8.40	7.74	14.14	38.7	41.3	29.8	30.3
Operating Profit	(8.40)	(7.74)	(14.14)	(38.7)	(41.3)	(29.8)	(30.3)
Interest Income	1.04	0.46	0.06	2.1	4.2	2.9	1.6
Pretax Income	(7.36)	(7.28)	(14.08)	(36.6)	(37.2)	(26.9)	(28.7)
Taxes	0.00	0.00	0.00	0.0	0.0	0.0	0.0
NI	(7.36)	(7.28)	(14.08)	(36.6)	(37.2)	(26.9)	(28.7)
Shares	67.26	68.75	69.84	43.2	62.5	64.5	69.8
EPS	$ (0.11)	$ (0.11)	$ (0.20)	$ (0.85)	$ (0.59)	$ (0.42)	$ (0.41)
Cash	28.58	24.02	15.89	83.90	59.47	34.93	15.89
AR + OR	0.31	0.24	0.27	0.41	0.48	0.28	0.27
Prepaids	1.75	1.62	1.13	2.84	1.49	0.94	1.13
TCA	30.64	25.88	17.29	87.15	61.44	36.15	17.29
							0.00
PPE	0.30	0.26	0.24	0.36	0.30	0.34	0.24
Intangibles	0.19	0.17	0.00	0.38	0.29	0.21	0.00
TNCA	0.49	0.43	0.24	0.74	0.59	0.55	0.24
TA	31.13	26.31	17.53	87.89	62.03	36.70	17.53
							0.00
AP + Accrued	8.85	9.43	6.92	4.86	9.33	8.04	6.92
c lease liabiliies	0.02	0.02	0.03	0.05	0.05	0.02	0.03
derivative liability	2.05	1.36	0.00	6.66	0.42	0.24	0.00
TCl	10.92	10.81	6.95	11.57	9.80	8.30	6.95
							0.00
lease libility	0.15	0.14	0.13	0.07	0.02	0.16	0.13
TNCL	0.15	0.14	0.13	0.07	0.02	0.16	0.13
TL	11.07	10.95	7.08	11.64	9.82	8.46	7.08
							0.00
SE	20.06	15.36	10.45	76.25	52.21	28.25	10.45
Funded Debt	0.17	0.16	0.16	0.12	0.07	0.18	0.16
Net Cash	28.41	23.86	15.73	83.78	59.40	34.76	15.73
Model NI	(7.36)	(7.28)	(14.08)	(36.55)	(37.18)	(26.88)	(28.72)
Reported NI	(9.18)	(6.59)	(28.50)	(31.64)	(30.93)	(28.13)	(44.27)
depreciation	0.04	0.04	0.11	0.14	0.14	0.16	0.19
amortization	0.02	0.02	0.21	0.08	0.08	0.08	0.25
SBC	0.90	1.81	11.13	8.50	5.01	4.16	13.84
Unrealized gain on FX	(0.49)	(0.15)	(0.29)	0.01	(2.92)	(0.76)	(0.93)
Accretion on lease	0.01	0.01	0.02	0.01	0.01	0.02	0.03
Receivables	(0.04)	0.08	0.09	(0.19)	(0.07)	0.20	0.12
prepaids	(0.81)	0.13	(0.07)	(2.15)	1.35	0.55	(0.75)
AP + Accrued	0.81	0.58	(1.75)	2.39	4.47	(1.29)	(0.36)
WC	0.44	2.51	9.44	8.79	8.07	3.12	12.40
CFFO	(8.74)	(4.08)	(19.06)	(22.85)	(22.86)	(25.01)	(31.87)
							0.00
CAPEX	(0.00)	(0.00)	(0.02)	(0.01)	(0.08)	(0.06)	(0.02)
CFFI	(0.00)	(0.00)	(0.02)	(0.01)	(0.08)	(0.06)	(0.02)
							0.00
options exercised	0.09	0.09	0.18	2.84	0.00	0.00	0.36
lease payments	(0.01)	(0.01)	(0.03)	(0.05)	(0.05)	(0.06)	(0.05)
CFFF	0.08	0.08	0.15	2.79	(0.05)	(0.06)	0.31
							0.00
Change in cash (CIC)	(8.66)	(4.00)	(18.92)	(20.07)	(22.99)	(25.13)	(31.59)
FCF	(8.74)	(4.08)	(19.07)	(22.86)	(22.94)	(25.07)	(31.90)