CORENAL THERAPEUTICS

Cadrenal Therapeutics, Inc. NASDAQ: CVKD August 2023

Cautionary Statement Concerning Forward Looking Statements

This document contains forward-looking statements. In addition, from time to time, we or our representatives may make forward-looking statements orally or in writing. We base these forward-looking statements on our expectations and projections about future events, which we derive from the information currently available to us. Such forward-looking statements relate to future events or our future performance, including: our financial performance and projections; our growth in revenue and earnings; and our business prospects and opportunities. You can identify forward-looking statements by those that are not historical in nature, particularly those that use terminology such as "may," "should," "expects," "anticipates," "contemplates," "estimates," "believes," "plans," "projected," "predicts," "potential," or "hopes" or the negative of these or similar terms.

In evaluating these forward-looking statements, you should consider various factors, including: our ability to successfully develop and commercialize product candidates, our ability to raise capital when needed, and the competitive environment of our business. These and other factors may cause our actual results to differ materially from any forward-looking statement, including those risk factors disclosed in our Annual Report on Form 10-K for the year ended December 31, 2023 filed with the Securities and Exchange Commission on March 30, 2023. Forward-looking statements are only predictions. The forward-looking events discussed in this document and other statements made from time to time by us or our representatives may not occur, and actual events and results may differ materially and are subject to risks, uncertainties, and assumptions about us. We are not obligated to publicly update or revise any forward-looking statement, whether as a result of uncertainties and assumptions, the forward-looking events discussed in this document, and other statements made from time to time by us or our representatives may forward-looking statement, whether as a result of uncertainties and assumptions, the forward-looking events discussed in this document, and other statements made from time to time by us or our representatives may forward-looking events discussed in this document, and other statements made from time to time by us or our representatives might not occur.



Corporate Overview

Late-stage Drug with Orphan Drug and Fast track Designations

- Developing tecarfarin, a late-stage novel oral and reversible anticoagulant (blood thinner) to prevent heart attacks, strokes and deaths due to blood clots in patients with certain rare medical conditions where "Legacy" Vitamin K Antagonists (e.g. warfarin) have failed to achieve sufficiently reliable anticoagulation. These areas include:
 - End Stage Kidney Disease (ESKD) with Atrial Fibrillation (AFib)
 - Left Ventricular Assist Devices (LVADs)
 - Antiphospholipid Syndrome (APS)
- Tecarfarin was designed as a Vitamin K Antagonist specifically to solve warfarin's metabolism problem via an alternate pathway that is abundant and essentially insaturable, providing a much more reliable pharmacokinetic profile.
 - Orphan drug and Fast track designations for ESKD with AFib providing for 7-year marketing exclusivity
 - Phase III remaining for ESKD with AFib; pursuing development for patients with LVADs and/or APS
 - Tecarfarin has been evaluated in 11 clinical trials in 1,003 subjects and has generally been well-tolerated in healthy adult subjects and patients with chronic kidney disease (CKD).
 - Approximately \$90 million invested in clinical and regulatory work to date.
- U.S. market potential estimated in excess of \$2 billion for three focused rare medical condition indications.



TECARFARIN OPPORTUNITY





The Problem: Rare Medical Conditions Lacking Effective Anticoagulation

Tecarfarin is targeted for indications where warfarin <u>FAILS</u> to achieve sufficiently stable anticoagulation and DOACs (Eliquis-class drugs) are <u>NOT</u> widely prescribed for these rare medical conditions.

• In 1954, warfarin, first developed as a rat poison, was approved to treat and prevent blood clots.

- Warfarin was widely used until 2010 when Pradaxa was approved.
- Sub-optimal anticoagulation for the patients with certain rare medical conditions
- Between 2010-2015, the FDA approved the first innovations in 50+ years to treat and prevent blood clots.
 - o Direct Oral Anticoagulants (DOACs) Pradaxa, Xarelto, Eliquis and Savaysa
- DOACs are not prescribed for a wide range of indications, including implanted medical devices for heart diseases, such as left ventricular assist devices
 - No known ongoing clinical trials or future research for rare medical conditions



Tecarfarin Looks to Solve Warfarin's Major Problems

Tecarfarin potentially provides a more stable anticoagulation than warfarin due to its metabolism, thereby decreasing the risk of stroke and bleeding

Warfarin CHALLENGING TO CONTROL

despite nearly 70 years of experience

Metabolism via the cytochrome P450 pathway

Significant variability in PK due to genetic variants and competition with other drugs

X

MAJOR PROBLEM for patients with rare medical conditions

Variable/Unreliable anticoagulation in patients at high risk for thrombotic events



Tecarfarin SPECIFICALLY DESIGNED

to solve the warfarin metabolism problem

Metabolized via an alternate pathway that is abundant and essentially insaturable

Reliable, stable PK profile

STABLE ANTICOAGULATION with proven mechanism of action for patients with rare medical conditions

Tecarfarin Clinical Development Pipeline

Late-stage drug with orphan drug and Fast track designations

			Development Phase				
Program	Prioritized Target Indications	Regulatory Strategy/Status	Discovery	Preclinical	Phase I	Phase II	Phase III
	End Stage Kidney Disease with AFib	FDA Orphan Drug Designation Granted FDA Fast Track Designation Granted EMA Orphan Drug Application In Process					
Tecarfarin	farin Left Ventricular Assist Devices (LVADs)	Developing	-				
	Antiphospholipid Syndrome (APS)	Developing					



Large Addressable Market Opportunities for Rare Medical Conditions

U.S. market potential estimated in excess of \$2 billion for three focused rare medical condition indications





Premium Pay for High Value Cardiovascular Orphan Drugs

Track record of recent transactions for orphan drugs in cardiovascular space

CAMZYOS

ر^{ال} Bristol Myers Squibb

 $Fold_{\mathbb{R}} \longrightarrow \mathbb{Q}P_{fizer}$

Developed by MyoKardia and the company was subsequently acquired by BMS for \$13 billion

Developed by FoldRx with \$88 million in private financing, before FoldRx was subsequently acquired by Pfizer

FDA DESIGNATIONS	Orphan Drug, Priority Review	FDA DESIGNATIONS	Orphan Drug, Fast Track, Priority Review & Breakthrough Therapy
EXPEDITED APPROVAL	Based on a <u>251-patient study called EXPLORER</u> , in which patients randomized to take the drug had significantly better peak oxygen consumption and improved on a widely used measurement of heart failure when compared to those who got a placebo.	EXPEDITED APPROVAL	Based on ATTR-ACT trial (Transthyretin Amyloidosis Cardiomyopathy Clinical Trial) - randomized 441 patients to tafamidis or placebo for 30 months
INVESTIGATORS ASSESSED	The primary composite functional endpoint, assessed at 30 weeks, was defined as the proportion of patients who achieved either improvement of peak oxygen consumption (pVO_2) by $\geq 1.5 \text{ mL/kg/min plus}$ improvement in NYHA class by at least 1 or improvement of pVO_2 by $\geq 3.0 \text{ mL/kg/min plus}$ no worsening in NYHA class.	INVESTIGATORS ASSESSED	All-cause mortality followed by CV hospitalizations
PRICE	\$89,500 a year (\$245/day) – one of the most expensive CV dru g	PRICE	\$225,000 a year (\$616/day) - the most expensive CV drug
NOTABLY	The approval came with a warning for the risk of heart failure and an FDA-mandated plan to manage that risk.	YEAR 2 SALES FOLLOWING LAUNCH	\$1.3 billion collectively for Vyndaqel [®] and Vyndamax [®]



Why Tecarfarin Now?

Tecarfarin is targeted for indications where warfarin <u>FAILS</u> to achieve sufficiently stable anticoagulation and DOACs (Eliquis-class drugs) are <u>NOT</u> widely prescribed for these rare medical conditions.

- 1. Certain rare medical conditions requiring chronic anticoagulation where warfarin has been unreliable, and DOACs (Eliquis-class drugs) are either contraindicated or not prescribed for these conditions.
- 2. Tecarfarin provides potentially more stable anticoagulation than warfarin because of its metabolism, thereby decreases the risk of stroke and bleeding.
- 3.) Retrometabolic drug design process targets a different metabolic pathway from the one targeted by warfarin.
- 4.
- Provides stable and effective anticoagulation based on studies demonstrating stable INR.
- 5. Tecarfarin's pharmacokinetics (renal clearance and plasma half-life) were not significantly affected by severe renal impairment. In contrast, warfarin clearance was substantially reduced resulting in a significant increase in half-life based on a head-to-head PK study.
- 6. Newest class anticoagulants (Factor XIs) are still in development and are not being pursued for these rare medical conditions.



CLINICAL DATA





Vitamin K Antagonism Inhibits Multiple Factors (II, VII, IX, X, Proteins C & S) in the Clotting Cascade vs. Single Targets of Newer Agents

Proven mechanism of action resulting in clinically meaningful anticoagulation in certain conditions where DOACs have failed



Tecarfarin is Designed to be an Improvement to Warfarin

Tecarfarin is more effective in certain patient subgroups

Tecarfarin was as effective as warfarin in patients with normal renal function

Randomized, doubleblind clinical trial

> **N=607** Patients with indications for chronic anticoagulation

Tecarfarin (n = 304) Warfarin (n = 303)

Percent Time in Therapeutic Range tends to favor Tecarfarin in multiple patient subgroups



Whitlock RP, Fordyce CB, Midei MG, et al. A randomized, double blind comparison of tecarfarin, a novel vitamin K antagonist, with warfarin. The EmbraceAC Trial. Thromb Haemost. 2016;116(2):241-250. doi:10.1160/TH15-11-0910



Kidney Failure Had a Significant Impact on Warfarin PK vs Tecarfarin

Tecarfarin metabolism not as impacted by kidney failure



Albrecht D, Turakhia MP, Ries D, et al. Pharmacokinetics of Tecarfarin and Warfarin in Patients with Severe Chronic Kidney Disease. *Thromb Haemost.* 2017;117(11):2026-2033. doi:10.1160/TH16-10-0815



Despite the Significantly Increased Risk of Stroke in ESKD pts with AFib, Most Patients are Not Anticoagulated Due to the Lack of Evidence of Benefit



1. Yoon CY, Noh J, Jhee JH, et al. Warfarin Use in Patients With Atrial Fibrillation Undergoing Hemodialysis: A Nationwide Population-Based Study. Stroke. 2017;48(9):2472-2479. doi:10.1161/STROKEAHA.117.017114

2. Randhawa MS, Vishwanath R, Rai MP, et al. Association Between Use of Warfarin for Atrial Fibrillation and Outcomes Among Patients With End-Stage Renal Disease: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(4):e202175. doi:10.1001/jamanetworkopen.2020.2175



Dabigatran Versus Warfarin in Patients with Mechanical Heart Valves EXCESS RISK AND NO BENEFIT



Trial terminated prematurely

due to an excess of thromboembolic and bleeding events among patients in the **dabigatran group**

	Dabigatran	Warfarin
	N=168	N=84
	N (%)	n (%)
Ischemic or unspecified stroke	9 (5.4)	0
Major bleeding	7 (4.2)	2 (2%)



Dose adjustment or discontinuation of dabigatran (as-treated analysis)



Antiphospholipid Syndrome (APS) Patients Randomized to DOACs Have Increased Arterial Thrombosis Risk

While VKA is preferred therapy patients with APS treated with Warfarin have high rates of recurrent thrombosis



RESULTS

Use of DOACs compared with VKAs was associated with:

- Increased odds of arterial thrombotic events, especially stroke
- No change in the odds of VTE or major bleeding
- Results were consistent within subgroups

Khairani CD, Bejjani A, Piazza G, et al. J Am Coll Cardiol. 2023;81(1):16-30. doi:10.1016/j.jacc.2022.10.008



UPCOMING MILESTONES





Accomplishments, Goals and Future Milestones

Accomplishments

Received Orphan Drug Designation for the prevention of systemic thromboembolism of cardiac origin in patients with ESKD and AFib.



Granted Fast Track designation for the prevention of systemic thromboembolism of cardiac origin in patients with ESKD and AFib.



Completed Initial Public Offering in January 2023 and Follow-On Offering to Raise a Combined \$14.5 million in 2023



Expanded focus for tecarfarin development for patients with implanted medical devices for heart diseases

Trial Design for Antiphospholipid Syndrome

Advance CMC/Manufacturing program

Licensing and Partnership Developments

Commence a Registration Study

Future Goals and Milestones

Trial Design for Left Ventricular Assist Devices (LVADs)





H2

2023

2024

2024



MANAGEMENT, BOARD & SCIENTIFIC ADVISORY BOARD





Leadership Team

Quang Pham CEO & Founder, Chairman	ESPERO D+RLATHIAN Genentech
Douglas Losordo, MD Chief Medical Officer	LONGEVERON VIENCES CALACIÓNS BIOSCIENCES CIENCES NYULANGONE BIOSCIENCES NYULANGONE MEDICAL CENTER Northwestern University
Matthew Szot, CPA Chief Financial Officer	SENESTECH ONVOLOSCIENCE RIPCURIC KPMG
John R. Murphy Director	EXAMPRIA Materials X A P R I A
Steven Zelenkofske, DO Director	AstraZeneca sanofi aventis Scientific UNOVARTIS SwanBio
Glynn Wilson, PhD Director	JUPITER WELLNESS SmithKline Beecham
Robert Lisicki Director	REGENERON O Daiichi-Sankyo AMCEN



Scientific Advisory Board (SAB)

Christopher Granger, MD	 Professor of Medicine in the Division of Cardiology at Duke University Member, Duke Clinical Research Institute (DCRI) 	Duke
Sean Pokorney, MD, MBA	• Electrophysiologist and Assistant Professor of Medicine	Duke
Elaine M. Hylek, MD, MPH	 Professor of Medicine, Boston University School of Medicine Director of the Thrombosis and Anticoagulation Service at Boston Medical Center (BMC) 	BOSTON UNIVERSITY
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Richard Whitlock, MD	 Cardiac Surgeon and Professor of Surgery, McMaster University Medical Center Investigator, Population Health Research Institute 	McMaster University
A. Michael Lincoff, MD	 Vice Chairman, Dept. of Cardiovascular Medicine, Cleveland Clinic Director of Clinical Research, Lerner Research Institute 	Cleveland Clinic



FINANCIALS & HIGHLIGHTS





Financial Summary

Cap Table (as of 8/10/23)

Cash (at 8/10/23)	\$9.6 million
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Debt	NONE
Common Shares Outstanding (excluding pre-funded warrants)	13,022,754
Pre-Funded Warrants	<u>2,985,715</u>
As Adjusted – Common Shares Outstanding	16,008,469
Warrants – Investors (avg. \$1.75)	4,285,715
Warrants - Underwriter & Placement Agt. Warrants (avg. \$2.68)	389,071
Stock Options Outstanding (avg. \$0.86)	1,175,000

Q2 2023 Financial Results

Operating Expenses (excluding non-cash items)	\$834,605
Market Capitalization	
As of 8/10/23	\$11.9 million
Insider Ownership (Common Stock)	
Insider Ownership as Percent of Shares Outstanding	47%



Summary of Highlights



PORTFOLIO

- Late-stage orphan drug candidate with IP rights in North America, Europe, Australia, Asia and Africa
- One 7-year U.S. orphan drug marketing exclusivity potential upon orphan drug approval

R&D

 Retrometabolic design eliminates or minimizes the CYP450 metabolism in the liver

REGULATORY

- FDA orphan drug designation of tecarfarin for patients with ESKD + AFib
- o FDA Fast Track designation
- Pursuing possible use for patients with left ventricular assist devices (LVADs) and Antiphospholipid Syndrome (APS)

CLINICAL

- Expected single pivotal Phase 3 placebo-controlled trial remaining for tecarfarin (N=492), based on latest FDA correspondence
- Existing safety database with 1,003 subjects in 11 clinical trials

COMMERCIAL

 More than \$2 billion U.S. annual market potential for tecarfarin drug candidate





Contact Us

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APPENDIX

Warfarin vs Tecarfarin Metabolism Pathways

Tecarfarin provides potentially a more reliable anticoagulation than warfarin because of its metabolism, thereby decreases the risk of stroke and bleeding.

Warfarin Metabolism via CYP450 is Complicated by Known Competitors, Inhibitors and Inducers and the Established Impact of Genetic Variants

Enzymes	Substrates	Inhibitors	Inducers
СҮР ЗА4	amlodipine, simvastatin, warfarin, amiodarone, sildenafil, midazolam, fluoxetine, haloperidol, codeine, oxycodone, methadone, fentanyl	ciprofloxacin, ketoconazole, ritonavir, methylprednisone, imatinib, tamoxifen, cimetidine, grapefruit juice	simvastatin, efavirenz, pentobarbital, carbamazepine, phenobarbital, phenytoin, valproic acid, caffeine
CYP IA2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	ciprofloxacin, enoxacin, fluvoxamine, oral contraceptives, phenylpropanolamine	montelukast, phenytoin, smoking components of cigarettes
CYP 2C8	repaglinide, paclitaxel, methadone	gemfibrozil, fluvoxamine, ketoconazole, trimethoprim	rifampin
СҮР 2С9	celecoxib, warfarin , phenytoin	amiodarone, fluconazole, miconazole, oxandrolone, capecitabine, etravirine, fluvastatin, metronidazole, Sulfinpyrazone, tigecycline	carbamazepine, rifampin, aprepitant, bosentan, phenobarbital, St. John's wort
CYP 2D6	lidocaine, metoprolol, haloperidol, fluoxetine, amitriptyline, metoclopramide, codeine, oxycosone, tramadol	amiodarone, chlorpromazine, citalopram, bupropion	rifampin, dexamethasone

Tecarfarin is Metabolized in the Human CarboxylEsterase 2 pathway (CES2

Enzymes	Substrates	Inhibitors	Inducers
CYP 3A4	amlodipine, simvastatin, warfarin, amiodarone, sildenafil, midazolam, fluoxetine, haloperidol, codeine, oxycodone, methadone, fentanyl	ciprofloxacin, ketoconazole, ritonavir, methylprednisone, imatinib, tamoxifen, cimetidine, grapefruit juice	simvastatin, efavirenz, pentobarbital, carbamazepine, phenobarbital, phenytoin, valproic acid, caffeine
CYP IA2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	ciprofloxacin, enoxacin, fluvoxamine, oral contraceptives, phenylpropanolamine	montelukast, phenytoin, smoking components of cigarettes
CYP 2C8	repaglinide, paclitaxel, methadone	gemfibrozil, fluvoxamine, ketoconazole, trimethoprim	rifampin
CYP 2C9	celecoxib, warfarin , phenytoin	amiodarone, fluconazole, miconazole, oxandrolone, capecitabine, etravirine, fluvastatin, metronidazole, Sulfinpyrazone, tigecycline	carbamazepine, rifampin, aprepitant, bosentan, phenobarbital, St. John's wort
CYP 2D6	lidocaine, metoprolol, haloperidol, fluoxetine, amitriptyline, metoclopramide, codeine, oxycosone, tramadol	amiodarone, chlorpromazine, citalopram, bupropion	rifampin, dexamethasone

CES2 Substrate Drugs

Antiplateletes/AnticoagulantsAcetylsalicylic acid

Angiotensin receptor blockers

Dabigatran etexilate

Candesartan cilexetil

Azilsartan medoxomil

Antivitral agents

Tenfovir disoproxil

Adefovir dipivoxil

Valacyclovir

Olmesartan medoxomil

Prasugrel

- Cocaine
 - Heroin

CNS agents

6-monoacetylmorphine

Immunosuppressive agents

- Methylprednisolone sodium succinate
- Deflazacort

Oncology agents

- Irinotecan
- Capecitabine

Anesthetic drug

Procaine

Limited Substrates Identified

Genetic variation exists, but limited evidence of clinical impact

Tecarfarin Shows TTR Above Anticoagulation Control Threshold

Tecarfarin provides stable anticoagulation

- Phase 2/3 Trial Design
- o Tecarfarin vs. well-controlled warfarin trial
- Randomized, double-blind trial designed to compare the quality of anticoagulation
- Average TTR as measured by the International Normalized Ratio (INR)
- Dosing managed by a centralized dose control center

Key Tecarfarin Findings:

Demonstrated TTR >72% overall and across key subgroups Demonstrated trends suggesting **improved TTR control** in key subgroups expected to do poorly with warfarin

Demonstrated **similar major bleeding** as warfarin and **no thrombotic events**

Tecarfarin percent time in therapeutic range (TTR)

TTR of 70% or greater

is generally accepted as the goal for stable anticoagulation with a VKA

Source: EmbraceAC Review by Whitlock et al., 2016

607 Patient Randomized Controlled Trial Shows Tecarfarin is Well-Tolerated for Stroke and Thrombus Prevention, with Fewer Hemorrhagic Events

Tecarfarin had fewer thrombotic events compared to warfarin

Randomized, doubleblind clinical trial

 N=607 Patients with indications for chronic anticoagulation
 Tecarfarin (n = 304)
 Warfarin (n = 303)

Tecarfarin treated subjects experienced <u>fewer</u> major hemorrhages than the warfarin treated patients

Whitlock RP, Fordyce CB, Midei MG, et al. A randomised, double blind comparison of tecarfarin, a novel vitamin K antagonist, with warfarin. The EmbraceAC Trial. Thromb Haemost. 2016;116(2):241-250. doi:10.1160/TH15-11-0910

Tecarfarin was Designed to be an Improvement to Warfarin

Tecarfarin was as effective as warfarin in patients with normal renal function Randomized, doubleblind clinical trial N=607 Patients with indications for chronic anticoagulation **Tecarfarin** (n = 304)**Warfarin** (n = 303)

Percent Time in Therapeutic Range

Whitlock RP, Fordyce CB, Midei MG, et al. A randomized, double blind comparison of tecarfarin, a novel vitamin K antagonist, with warfarin. The EmbraceAC Trial. Thromb Haemost. 2016;116(2):241-250. doi:10.1160/TH15-11-0910

Summary of Guidelines Recommendations on Anticoagulant Treatment Prescription in Patients with Antiphospholipid Syndrome

PATIENTS WITH DEFINITE APS

Tecarfarin Phase 1 PK Trial in Stage 4 CKD Patients Provides Evidence that CKD does not alter Tecarfarin exposure while Warfarin Exposure is Increased

Tecarfarin does not require any dose adjustments in renal impaired/CKD patients

Summary Table

% change between Stage 4 CKD patients vs healthy subjects matched for each drug using a randomized crossover design (n=23)

	Tecarfarin (% change)	(S)-Warfarin (% change)
AUC	+15%	+44%
C _{max}	+6%	+7%
t _{1/2}	-8%	+19%

Result Highlights

	Tecarfarin	Warfarin
(•	 Elimination from the body was not affected by severe kidney dysfunction 	Exposure increased 44% in Stage 4 CKD patients
(•	Half-life and the amount of drug in the body were similar in Stage 4 CKD patients and healthy subjects	Plasma concentration and half-life increased in Stage 4 CKD patients

This study suggests that

tecarfarin does not require any dose adjustments in renal impaired/CKD patients

Tecarfarin Phase 3 Trial Design for ESKD and AFib

Tecarfarin vs. Placebo in Patients with ESKD and AFib

Randomized, Double-Blind, Placebo-Controlled (no active control)

