Cadrenal Therapeutics, Inc.

NASDAQ: CVKD

May 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 change the direction of the Company; our ability to keep pace with new technology and changing market needs; 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 Registration Statement on Form S-1 filed with the Securities and Exchange Commission on January 17, 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 might not occur.

CADRENAL THERAPEUTICS™

AGENDA

- **TECARFARIN OPPORTUNITY**
- MANAGEMENT, PRINCIPAL INVESTIGATOR & SCIENTIFIC ADVISORY BOARD
- UPCOMING MILESTONES
- CLINICAL DATA

CADRENAL Investment Case

CADRENAL THERAPEUTICS' **asset,**

tecarfarin

POSITIONED FOR FINAL, CONFIRMATORY PHASE 3 STUDY

to establish the indication of **prevention of systemic thromboembolism in patients with end-stage renal disease and atrial fibrillation**

ESRD + AFib

There are NO EFFECTIVE TREATMENT OPTIONS for patients with ESRD + AFib

UP TO **$1B**	Peak U.S. annual market potential for **tecarfarin** for orphan indication[1]
$90M	Invested to date
11	Clinical trials
>1,000	Subjects

FDA Designations:

- **Orphan Drug** 2019
- **Fast Track** 2023

Planned pivotal clinical trial:
492 subjects with one year of follow up

- First patient in (FPI) to last subject final visit approximately 2 years, 3 months
- Under Fast Track rolling submission anticipate NDA complete in under 3 years from study start

1. Based upon 2019 study, adjusted for inflation.

CADRENAL THERAPEUTICS

Tailored Regulatory Pathway for Patients with ESRD + AFib

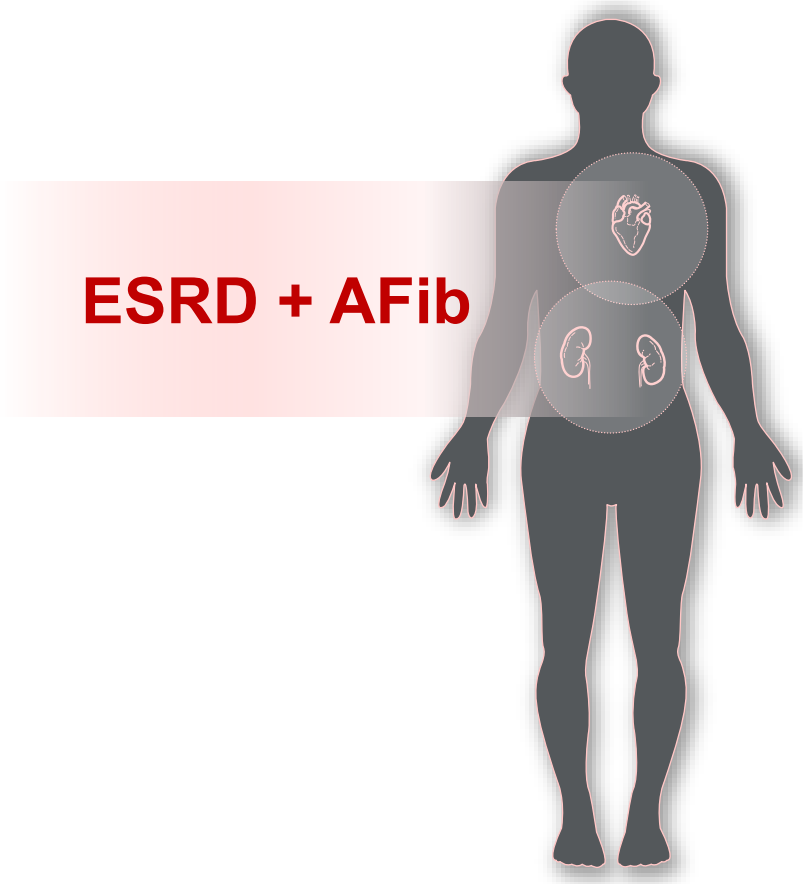
Cadrenal intends to **follow the FDAs guidance** (which granted tecarfarin orphan drug designation and subsequently granted Fast Track Designation) **and that of industry leading cardiologists and nephrologists** to **pursue approval for tecarfarin in patients with ESRD + AFib** to meet the widely acknowledged lack of effective alternative treatment options for this patient population.

Regulatory Pathway For Tecarfarin

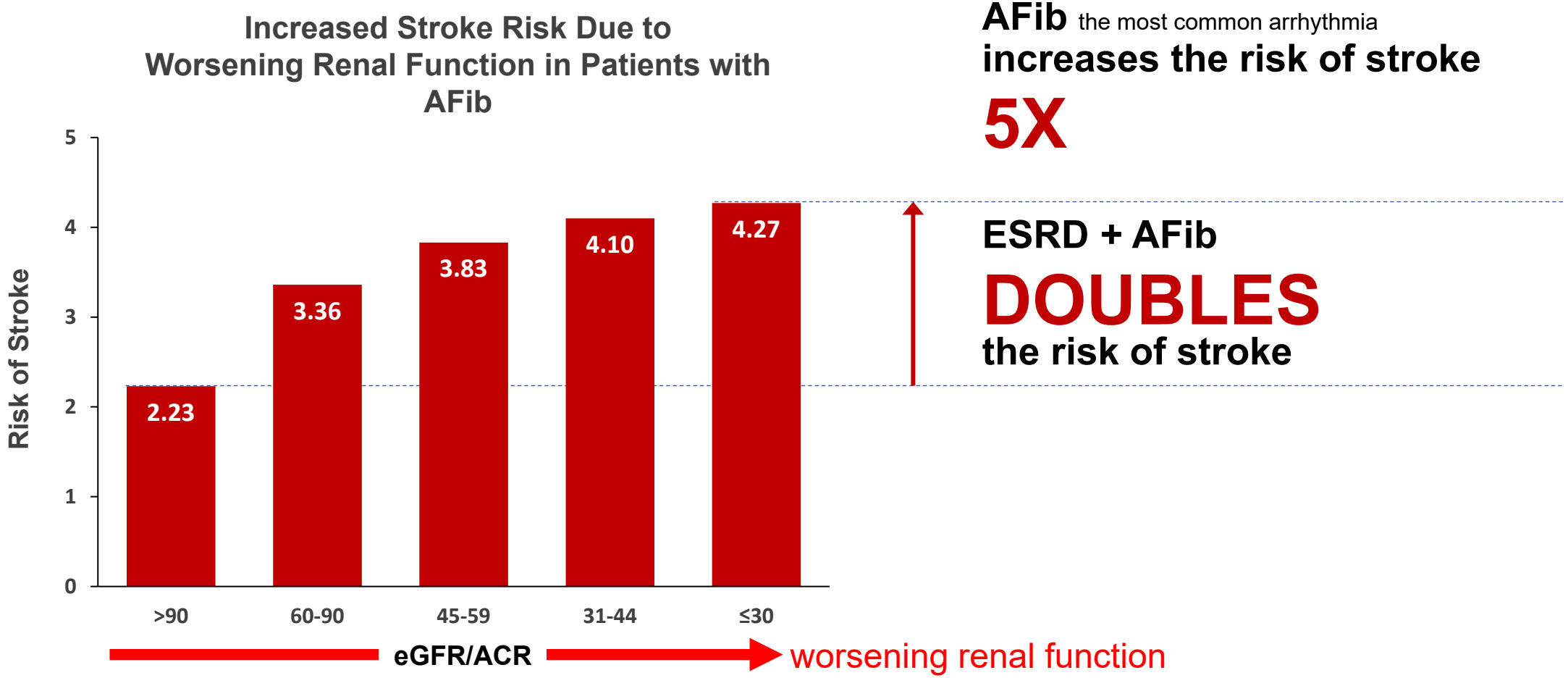
Broad Label, All OAC Indications	Broad Label, All OAC Indications With "Enriched Population"	Orphan Drug Designation For ESRD Patients With AFib
2006-2017	**2017-2019**	**2019-Current**
• ARYx Therapeutics (2006-2011) • Armetheon (2011-2017)	• Espero BioPharma (2017-2019)	• Espero BioPharma (2019-2020) • Cadrenal Therapeutics (January 2022 to Current)

THE PROBLEM

No effective anticoagulant treatment options
for patients with
End-Stage Renal Disease AND Atrial Fibrillation



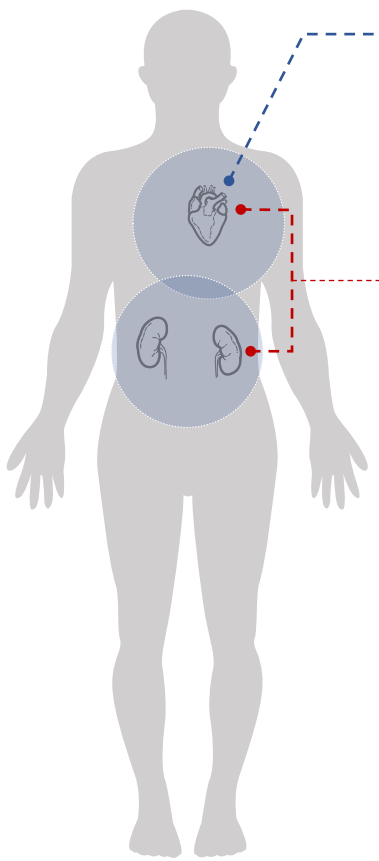
The presence of either chronic kidney disease (CKD) or AFib increases the risk of serious thromboembolic adverse clinical outcomes, such as stroke and death



Trevor Mace-Brickman et al, The Risk of Stroke and Stroke Type in Patients With Atrial Fibrillation and Chronic Kidney Disease, *Canadian Journal of Kidney Health and Disease*, 2019, Volume 6: 1–9.

CARDRENAL THERAPEUTICS

Antithrombotic therapy is typically recommended to decrease this risk of stroke in AFib patients

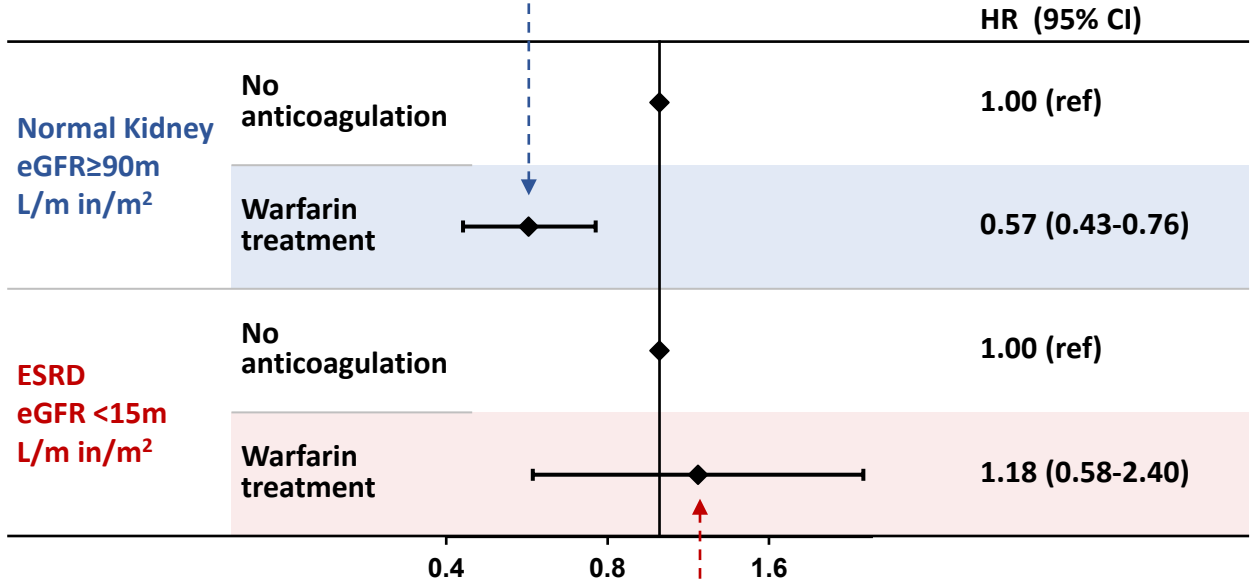


AFib patients
Antithrombotic Therapy

ESRD + AFib patients
NO EFFECTIVE THERAPIES

Warfarin Treatment and Stroke Risk

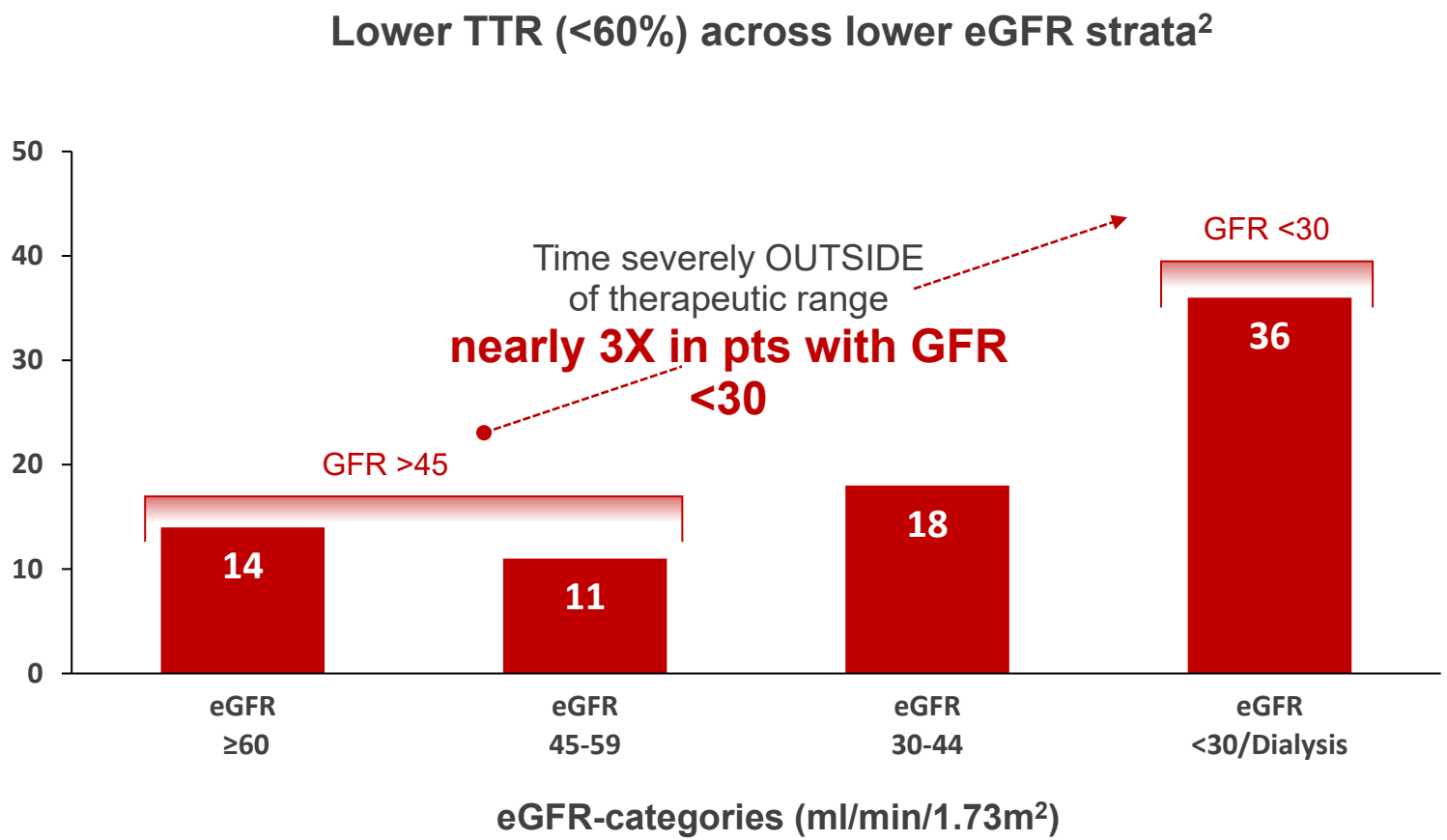
In normal kidney function, warfarin REDUCES stroke risk



In ESRD, warfarin DOES NOT REDUCE stroke risk[1]

Bonde AN, et al. Renal Function and the Risk of Stroke and Bleeding in Patients With Atrial Fibrillation: An Observational Cohort Study. *Stroke*. 2016;47(11):2707-2713. doi:10.1161/STROKEAHA.116.014422
1 https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2763969

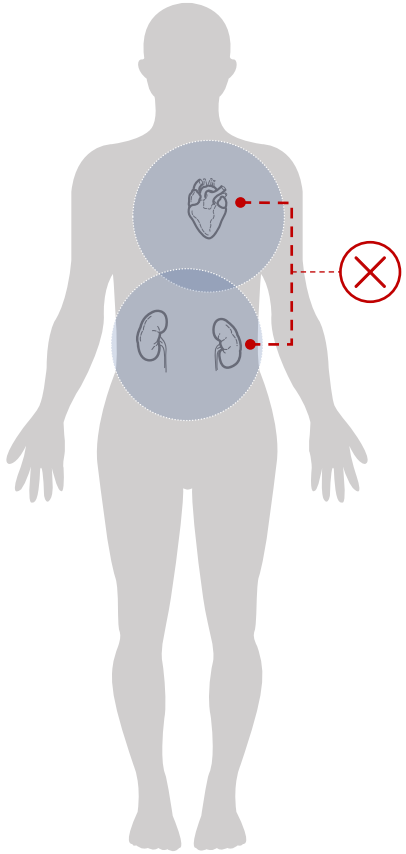
Warfarin (most common treatment) is difficult to control in ESRD patients due to metabolism via cytochrome P450 pathway[1]



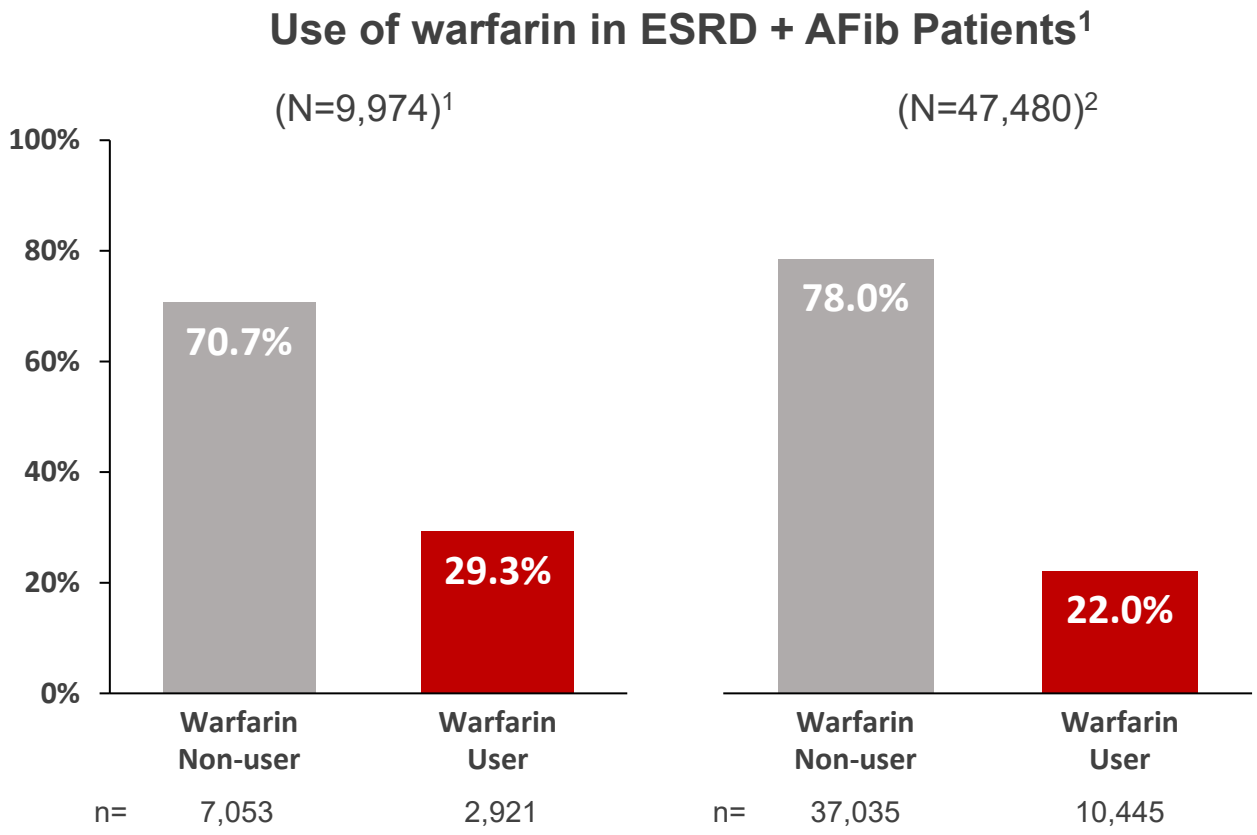
1. Mandeep S. et al, Association Between Use of Warfarin for Atrial Fibrillation and Outcomes Among Patients With End-Stage Renal Disease. A Systematic Review and Meta-analysis. *JAMA Network Open*. 2020;3(4):e202175.
2. Szummer K, Gasparini A, Eliasson S, et al. Time in Therapeutic Range and Outcomes After Warfarin Initiation in Newly Diagnosed Atrial Fibrillation Patients With Renal Dysfunction. J Am Heart Assoc. 2017;6(3):e004925. Published 2017 Mar 1. doi:10.1161/JAHA.116.004925

CARDRENAL THERAPEUTICS

Despite the significantly increased risk of stroke in ESRD with AFib, most patients are not given warfarin due to the lack of evidence of benefit



Most patients with ESRD + AFib <u>are not prescribed</u> ANY anticoagulation to reduce their risk of stroke



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

OUR SOLUTION

Tecarfarin

PHASE 3, FAVORABLE SAFETY PROFILE

TARGETS

Different metabolic pathway
than the most commonly prescribed drugs for the treatment of thrombosis and AFib

- Established **similar MOA to warfarin**
- Elimination from body was **not affected by severe kidney dysfunction**
- **Demonstrated TTR > 72%** vs anticoagulation control threshold of 70%

EVALUATED

11 clinical trials
over **1,003 subjects**

269 Patients treated for at least **6 months**

129 Patients treated for **one year or more**

WELL-TOLERATED

In Phase 1, Phase 2, and Phase 2/3 clinical trials, **healthy adult subjects and patients with CKD**

CADRENAL THERAPEUTICS

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

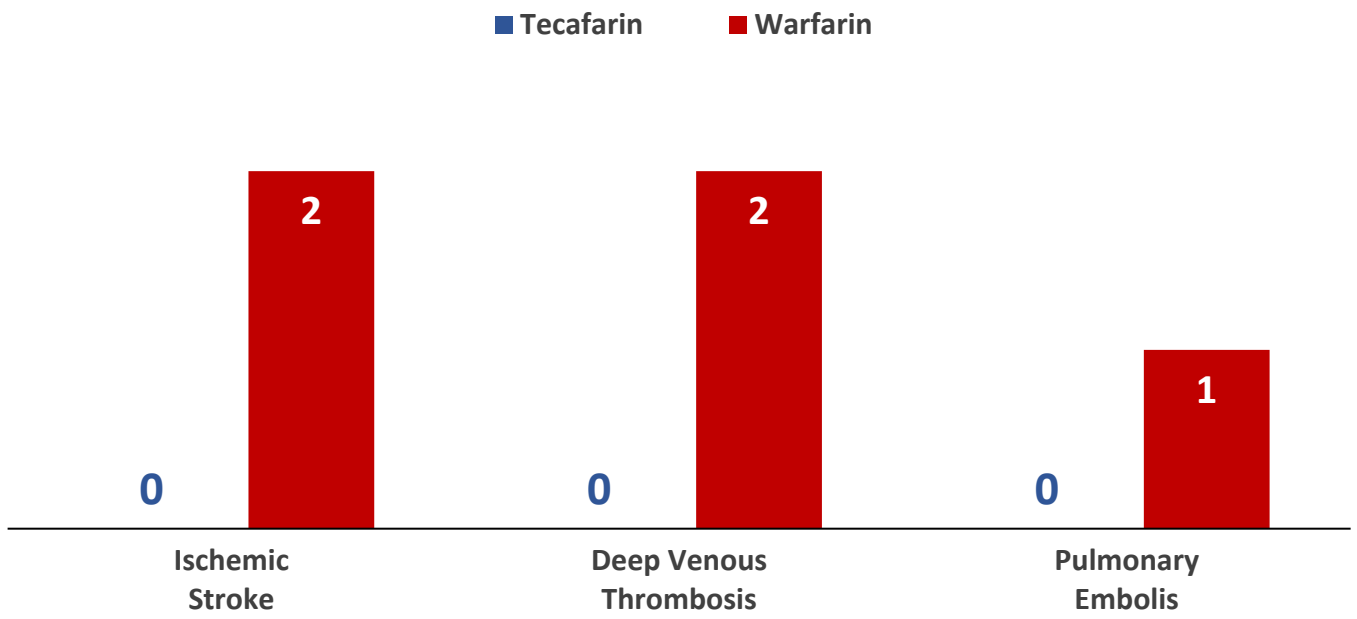
Tecarfarin had fewer thrombotic events compared to warfarin

Randomized, double-blind 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

CADRENAL THERAPEUTICS

Tecarfarin is Designed to be an Improvement to Warfarin

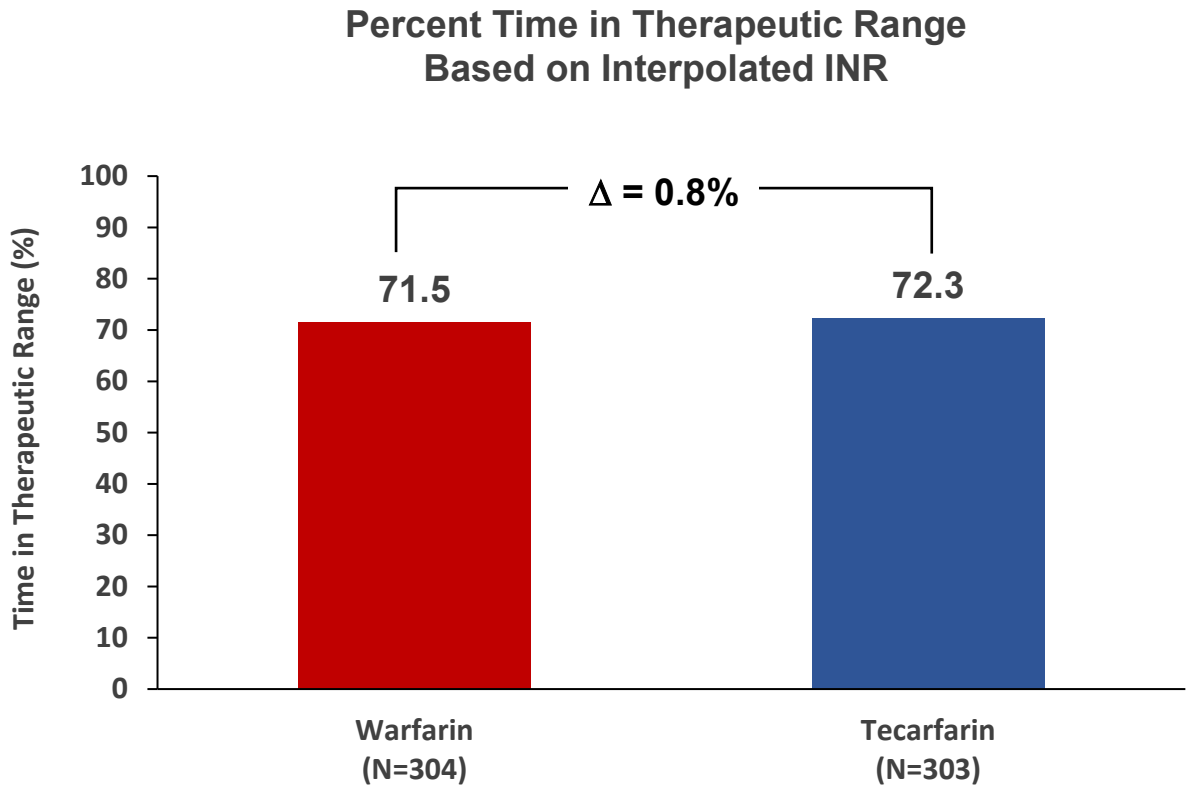
Tecarfarin was as effective as warfarin in patients with normal renal function

Randomized, double-blind clinical trial

N=607
Patients with indications for chronic anticoagulation

Tecarfarin (n = 304)

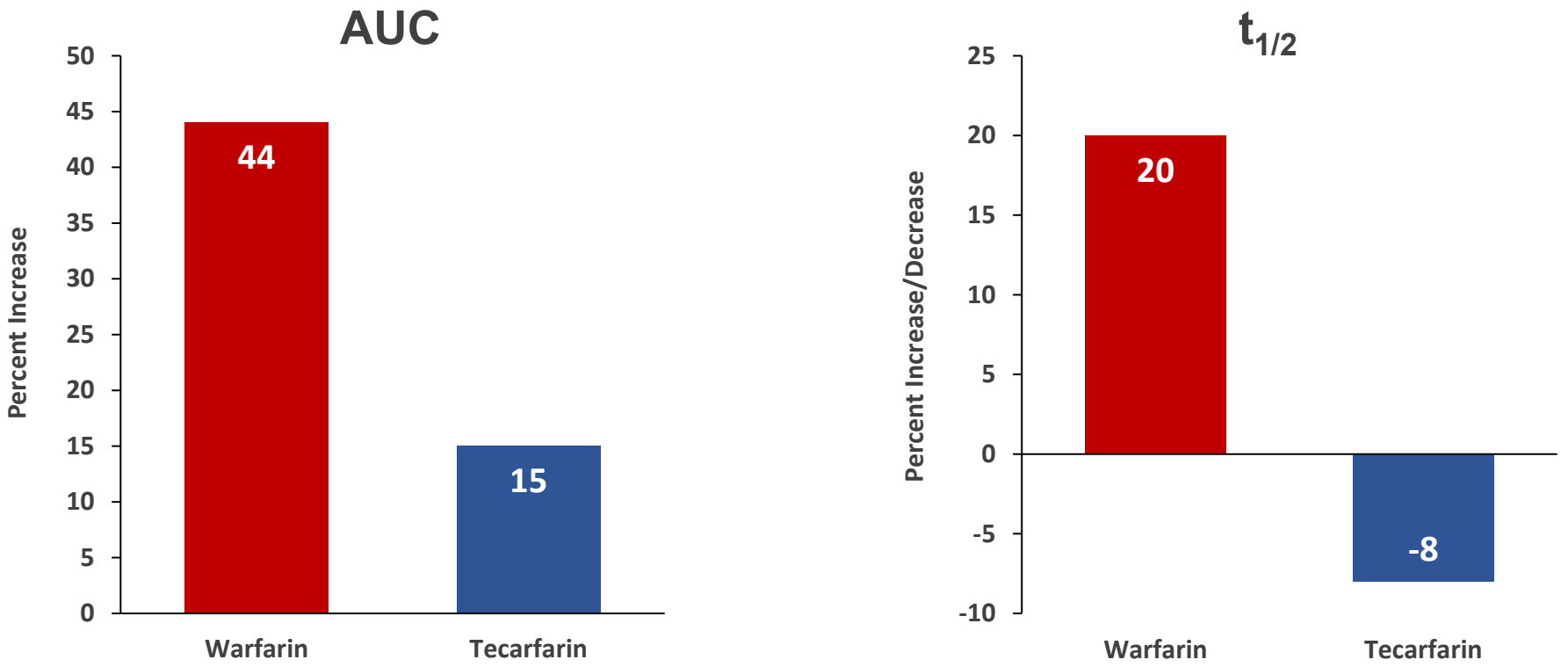
Warfarin (n = 303)



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

Renal Failure Had a Significant Impact on Warfarin PK vs Tecarfarin

Percent Increase in Exposure for Healthy Volunteer Subjects vs. Chronic Kidney Disease Subjects for (S)-Warfarin and Tecarfarin (n =23)



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

CADRENAL THERAPEUTICS

CADRENAL THERAPEUTICS™

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TECARAFIN OPPORTUNITY

MANAGEMENT, PRINCIPAL INVESTIGATOR & SCIENTIFIC ADVISORY BOARD

UPCOMING MILESTONES

CLINICAL DATA

Management

Quang Pham
CEO & Founder

Espero BioPharma

Lathian Systems

Genentech

Marine Corps

Douglas Losordo, MD
Chief Medical Officer

Cardiologist, Global Head of R&D

Director, Longeveron, Inc. (NASDAQ: LGVN)

CMO, KBP BioSciences, Inc.

CMO, Caladrius Biosciences (NASDAQ: CLBS)

Professor of Medicine, NYU Langone Medical Center and Northwestern University

Matthew Szot, CPA
Chief Financial Officer

S&W Seed Company (NASDAQ: SANW), CFO

INVO Bioscience (NASDAQ: INVO), Chairman of Audit Committee

SenesTech (NASDAQ: SNES), Chairman of Audit Committee

Rip Curl, Inc., CFO

KPMG

Principal Investigator and Scientific Advisory Board (SAB)

Sean Pokorney
MD, MBA
Principal Investigator

Cardiologist, electrophysiologist and researcher specializing in ESRD+AFib

Duke University and Duke Clinical Research Institute (DCRI)

SCIENTIFIC ADVISORY BOARD

Christopher Granger, MD
Professor of Medicine in the Division of Cardiology at Duke University
Member, Duke Clinical Research Institute (DCRI)

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)

C. Michael Gibson, MD
Professor of Medicine, Harvard Medical School
Interventional Cardiologist, Beth Israel Deaconess Medical Center
President & CEO, Baim Institute for Clinical Research

Wolfgang C. Winkelmayer, MD, MPH
Chief, Section of Nephrology, Professor of Medicine, Baylor University
Director, Selzman Institute for Kidney Health

Richard Whitlock, MD
Cardiac Surgeon and Professor of Surgery, McMaster University Medical Center
Investigator, Population Health Research Institute

A. Michael Lincoff, MD
Vice Chairman, Dept. of Cardiovascular Medicine, Cleveland Clinic
Director of Clinical Research, Lerner Research Institute

CADRENAL THERAPEUTICS™

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UPCOMING MILESTONES

CLINICAL DATA

Planned Phase 3 Study

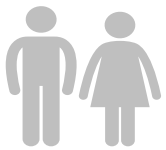
Expected to be the FINAL STUDY required to seek regulatory approval

- **ACTOR-AF Study**
  Anti-Coagulation with Tecarfarin on Outcomes in Renal Disease and Atrial Fibrillation
- **Phase 3 | 492 patients**
- **Randomized, Double-Blind, Placebo-Controlled Outcomes Study**
  - **Tecarfarin vs. Placebo** (not active control)
  - Subjects with End-Stage Renal Disease and Atrial Fibrillation not Currently Treated with Chronic Oral Anticoagulation

Tecarfarin Phase 3 Trial Design

Tecarfarin vs. Placebo in Patients with ESRD and AFib

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



Planned Enrollment
N = 492

ESRD (eGFR < 15 mL/min/1.73 mm^2) documented chronic paroxysmal, persistent or permanent AFib

Trial Sites:
U.S. and Canada, ROW TBD

R
1:1

Randomization stratified according to VKORC1 status

Tecarfarin (n = 246)

Placebo (n = 246)

12-month follow-up
for Primary Endpoint of time to combined endpoint of ischemic stroke or systemic embolism (80% power to detect a 25% treatment benefit)

CADRENAL THERAPEUTICS

U.S. ANNUAL MARKET POTENTIAL

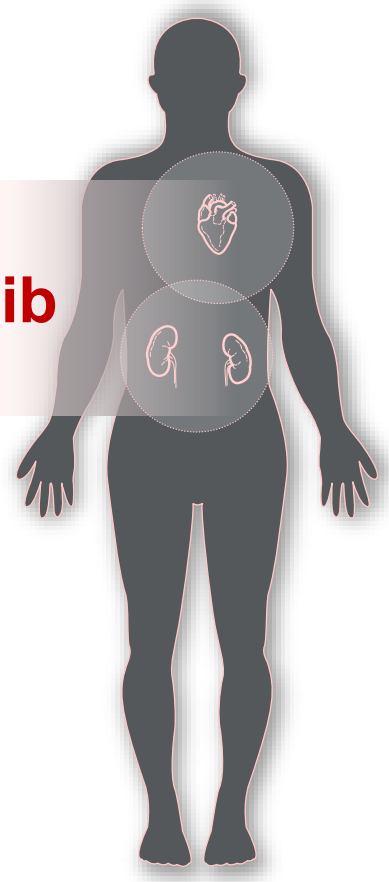
UP TO
$1 BILLION*

if approved by the FDA

Orphan Pricing

$65 per day (WAC) | **$23,400** annually

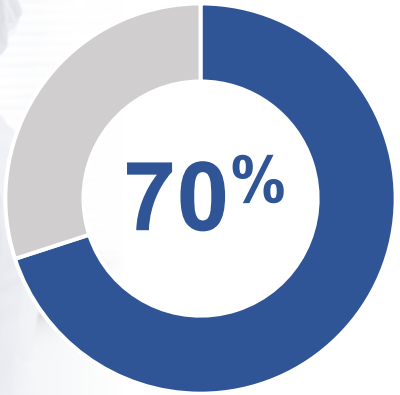
ESRD + AFib



*Based upon 2019 study, adjusted for inflation

CARDIORENAL THERAPEUTICS

Targeted Patient Commercialization Opportunity



Addressable patient population occurs at DaVita or Fresenius Dialysis Centers

Fresenius and DaVita operate 70% of the 6,800 outpatient dialysis centers in the U.S. on a combined basis

Once advancing to ESRD:

patients with ESRD+AFib receive dialysis 2-3 times a week

A study utilizing the Fresenius Medical Care North America ESRD database reported that some patients on dialysis received off-label dabigatran or rivaroxaban shortly after their marketing approval in the United States, and their use in this population was associated with poor outcomes

1. Source: DaVita Inc. 2020 Annual Report

CARDIORENAL THERAPEUTICS

Tafamidis: Cardiovascular Orphan Drug Case Study

Vyndaqel® (tafamidis meglumine) 20 mg capsules

Vyndamax™ (tafamidis) 61 mg capsules

VYNDAQEL® (tafamidis meglumine) and VYNDAMAX® (tafamidis) are novel oral cardiovascular drugs approved by U.S. FDA in May 2019 for the treatment of cardiomyopathy caused by transthyretin amyloidosis (ATTR-CM)

ATTR-CM is a rare disease caused by the buildup of a protein called amyloid, which is made of transthyretin, in the main pumping chamber of the heart – which ultimately leads to cardiomyopathy and progressive heart failure

FoldRx → Pfizer

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

FDA DESIGNATIONS	**Orphan Drug, Fast Track, Priority Review & Breakthrough Therapy**
EXPEDITED APPROVAL	Based on ATTR-ACT trial (Transthyretin Amyloidosis Cardiomyopathy Clinical Trial) - randomized 441 patients to tafamidis or placebo for 30 months
INVESTIGATORS ASSESSED	All-cause mortality followed by CV hospitalizations
PRICE	$225,000 a year ($616/day) - *the most expensive CV drug*
YEAR 2 SALES FOLLOWING LAUNCH	$1.3 billion collectively for Vyndaqel® and Vyndamax®

1. Vyndaqel contains the micronized meglumine salt of tafamidis, while Vyndamax contains the free acid form of tafamidis.

CARDIOVASCULAR THERAPEUTICS

Cap Table & Insider Ownership

Cap Table

Cash (3/31/23)	$4.0 million
Debt	NONE
Common Shares Outstanding	11,722,754
Preferred Shares Outstanding	NONE
Warrants - Underwriter	110,500
Stock Options Outstanding	1,100,000

Q123 Financial Results

Operating Expenses (excluding non-cash items)	$913,653

Insider Ownership (Common Stock)

Named Executive Officers and Directors	
Quang Pham, CEO	6,300,000
Matthew Szot, CFO	500,000
John Murphy, Board of Directors	594,792
Steven Zelenkofske, Board of Directors	40,000
Glynn Wilson, Board of Directors	50,000
All Executive Officers and Directors	**7,484,792**
Insider Ownership as Percent of Shares Outstanding	**64%**

Doug Losordo, CMO holds 300,000 options

CADRENAL THERAPEUTICS

Summary of Highlights

CADRENAL THERAPEUTICS™

ADVANTAGE

PORTFOLIO

- Phase 3 orphan drug candidate with IP rights in North America, Europe, Australia, Asia and Africa
- 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 (2019) of tecarfarin for patients with ESRD + AFib
- FDA Fast Track designation (2023)

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

- $1 billion U.S. annual market potential for tecarfarin drug candidate
- Over 70% of dialysis patients in the U.S. treated by two companies, DaVita and Fresenius

CADRENAL THERAPEUTICS™

CONTACT US

Quang Pham
CEO & Founder

Matthew Szot
CFO

CADRENAL THERAPEUTICS™

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UPCOMING MILESTONES

CLINICAL DATA

Retrometabolic Drug Design

Novel therapeutic agent with a proven mechanism of action and cleaner metabolic profile

Goal is to reduce risk of potential off-target and undesired side effects

Tecarfarin design:

Metabolic clearance not hindered by the body by eliminating or minimizing its metabolism in the liver, thus avoiding the Cytochrome P450 (CYP450) pathway

- We believe this may allow elimination by large capacity and non-saturable tissue esterase pathways that exist throughout the body rather than just in the liver
- Eliminates or minimizes the Cytochrome P450 (CYP450) metabolism in the liver
- Metabolizes to a pharmacologically inactive, non-toxic, and easily-excreted end-product, which we call the “ideal metabolite”
- Results in decreased risk/occurrence of drug-drug interactions and a we believe will result in safer clearance from the body

CADRENAL THERAPEUTICS

Tecarfarin Phase 1 PK Trial in Stage 4 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

CARDIOVASCULAR THERAPEUTICS

Tecarfarin Shows TTR Above Anticoagulation Control Threshold

Phase 2/3 Trial Design

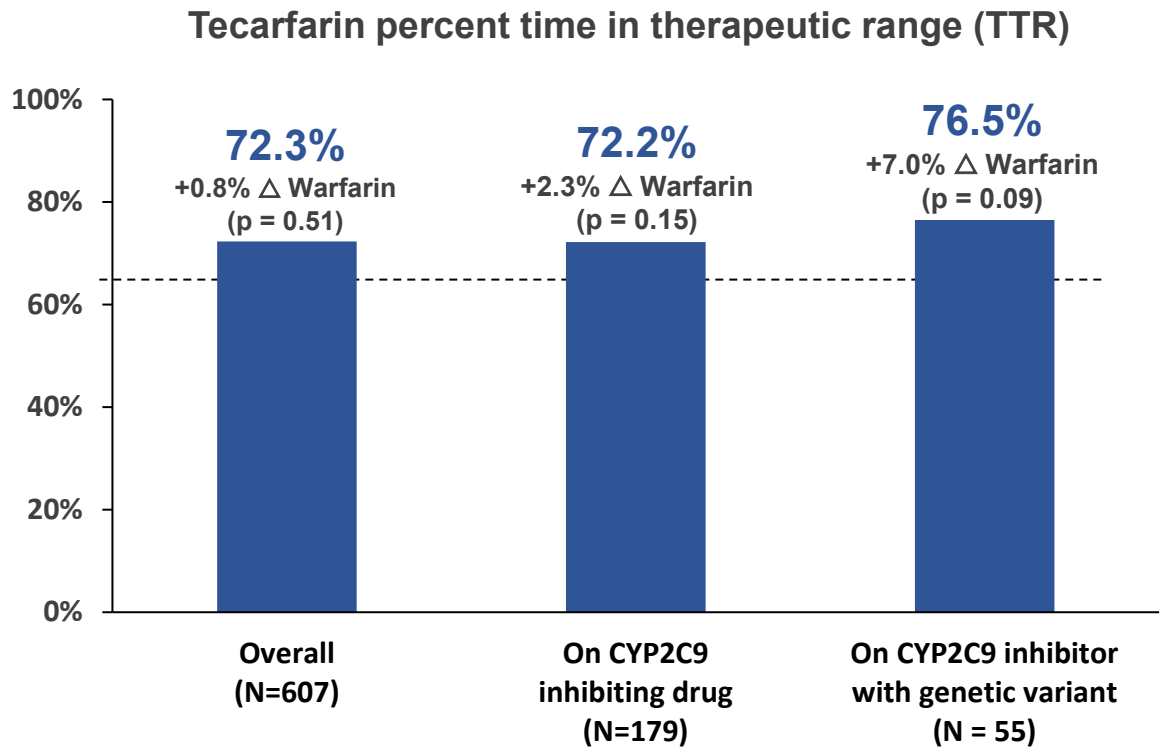
- Tecarfarin vs warfarin trial
- Randomized, double-blind trial designed to compare the quality of anticoagulation
- Average TTR as measured by the International Normalized Ratio (INR)
- Dosing managed by a centralized dose control center

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



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

CADRENAL THERAPEUTICS

Risk Factors Related to Our Business

Our business is subject to several risks you should be aware of before making an investment decision

These risks include the following:

- Our success is primarily dependent on the successful regulatory approval and commercialization of our lead product candidate
- Our approach to discovery and development is novel, unproven and may not result in a marketable product
- We have no source of predictable revenue, have incurred significant losses since inception, may never become profitable and may incur substantial and increasing net losses for the foreseeable future as we continue the development of, and seek regulatory approval for our product candidate
- If clinical trials of our product candidate fail to demonstrate safety and efficacy, we may be unable to obtain regulatory approvals to commercialize our product candidate
- We are subject to regulatory approval processes that are lengthy, time-consuming and unpredictable. We may not obtain approval for our product candidate from the FDA or foreign regulatory authorities
- Even if we obtain regulatory approval, the market may not be receptive to our product candidate
- We may not be able to establish collaborative partnerships with other pharmaceutical companies, through which we expect to complete development of, obtain marketing approval for and, if approved, manufacture and market our product candidate
- We may encounter difficulties satisfying the requirements of clinical trial protocols, including patient enrollment
- We may face competition from other companies in our field or claims from third parties alleging infringement of their intellectual property

Glossary of Terms

Term	Abbreviation
Atrial Fibrillation	AFib
Area Under the Curve	AUC
Chronic Kidney Disease	CKD
Maximum Serum Concentration	C_{max}
Chemistry, Manufacturing and Controls	CMC
End Stage Renal Disease	ESRD
Half Life	$t^{1/2}$
International Normalized Ratio	INR
Journal of the American Medical Association	JAMA
Left Ventricular Assist Device	LVAD
Major Adverse Cardiac Event	MACE
Mechanical Heart Valve	MHV
Mechanism of Action	MOA
New Drug Application	NDA
Oral Anticoagulation Therapy	OAC
Time in Therapeutic Range	TTR
Vitamin K Antagonist	VKA