Cereno Scientific Capital Markets Day

August 30, 2023

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Welcome and Introduction to Cereno CMD 2023

- Agenda – need around management of CVD, Cereno's portfolio, remarkable data, steady vision
- Q&A – open for questions from audience in-situ and on the web
- Participants

Today’s program

Sten R. Sörensen
Chief Executive Officer, Cereno

Dr. Björn Dahlöf
Chief Medical Officer, Cereno

Dr. Raymond Benza
System Director of Pulmonary Hypertension at Mount Sinai Icahn School of Medicine, New York City; Chair of SAB, Cereno, and PI for CS1’s Phase II study

Dr. Phil B. Adamson
Divisional Vice President and Chief Medical Officer Heart Failure Division, Abbott

Dr. Michael Holinstat
Ass. Prof. at University of Michigan Medical School; and Director Translation Research, Cereno

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Cereno’s Commitment to Transforming Cardiovascular Disease Management

Sten R. Sörensen
Chief Executive Officer (CEO), Cereno

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Cereno Scientific at ESC 2023

ESC Congress 2023 Amsterdam
Onsite & Online, 25-28 August

Most deaths worldwide are caused by cardiovascular disease

Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels.

22.2 million people

are expected to die annually due to CVD by 2030.

80% of CVD deaths

are due to heart attacks and strokes.

WHY?

Most CVD complications happen because of thrombus formation – blood clots obstructing the cardiovascular system.

Existing treatment options are insufficient.

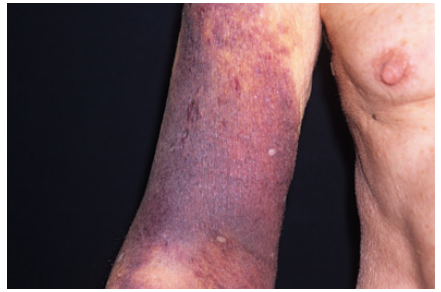
Sources: WHO Fact Sheet (link), European Heart Network (link), American Heart Association (link)

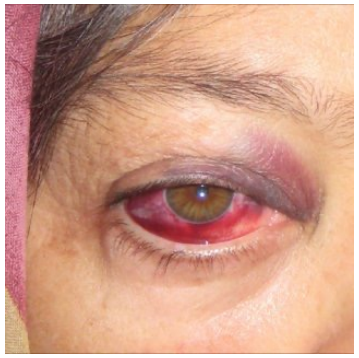
Bleeding risk with current anti-thrombotics impact patient lives significantly

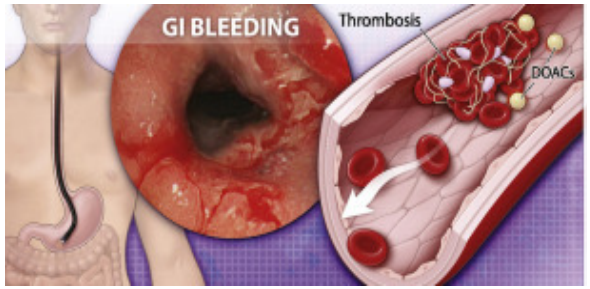
- **Bleeding is a major adverse event of current anti-thrombotic treatments.**
  - Fatal at times
  - Lead to reduced quality of life in survivors

- 46% patients die in-hospital due to approved novel anti-coagulants related brain hemorrhage.

- Up to 20-50% of VTE patients receiving anti-coagulant therapy to prevent recurrence have reported
  - major disability
  - poor quality of life and
  - fear of recurrences if therapy is disrupted temporarily





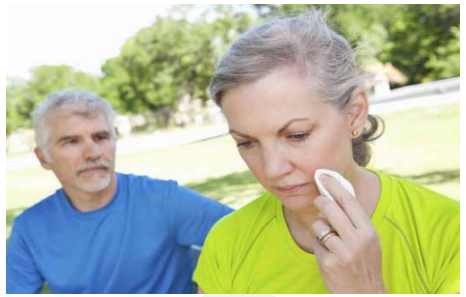


Source: Cipkar C. et.al 2019 (Link), S. Piran & S. Schuman, 2019 (Link), Freehan M. et.al. 2017 (Link)
For more information click to see slide #101, #102, #104, #106 .

PAH is a progressive debilitating chronic disease with no cure

- **Mean life expectancy is 2.5 years without therapy, now extended to 7.5 years with modern therapeutics**

- Today, there is No Cure for PAH except for Lung Transplantation



"I couldn't catch my breath to give a presentation or even to keep up with my peers walking down the hallway. It was very embarrassing and I would tell people that I was having a bad asthma day." *- A PAH patient from FDA's Voice of Patient Survey*

"I wasn't able to walk the 50 feet from my car to the elevator at my building or even up the stairs from my living room to my bedroom. I feel short of breath and lightheaded just walking around the house or trying to do normal household chores." *-A PAH patient from FDA's Voice of Patient Survey*

Source: 1. Dr. Benza, 2. FDA's Voice of Patients Survey (Link), 3. L. Guilevin et.al (Link) .
For additional information on FDA' Voice of Patient Survey, click here
Picture sources: Pulmonary Hypertension Article 2016, LinK; UCLA Health, State-of-the-art treatment for pulmonary arterial hypertension Link; Everyday Health Article (2023), Link

PAH significantly impact patients' daily quality of life

Significant impact on different aspects of patient's lives. A large proportion of PAH patients report difficulties with

Cereno develops novel drugs to transform treatments for PAH and other cardiovascular diseases

Introducing epigenetic modulation through HDAC inhibition with disease modifying potential.

Lead program CS1 currently in US Phase II in PAH with strong rationale and supportive data – topline data expected in Q1 2024.

Pipeline portfolio:

CS1: Phase II HDACi, ODD in PAH

CS585: Preclinical Prostacyclin Receptor Agonist

CS014: Preclinical HDACi

Cereno's global presence

HQ: Gothenburg, Sweden

US subsidiary: Boston, MA

CS1 Clinical Phase II: 10 centers in the US in collaboration with Abbott

Preclinical R&D collaboration: University of Michigan, MI

Listed on Nasdaq First North Growth Market since June 2023 (CRNO B)

Cereno's Scientific Advisory Board are top thought leaders in the field of CVD

Dr. Bertram Pitt
Chair of Board
Prof Em in Medicine, University of Michigan School of Medicine

Dr. Raymond L. Benza
System Director of Pulmonary Hypertension at Mount Sinai Icahn School of Medicine, New York City

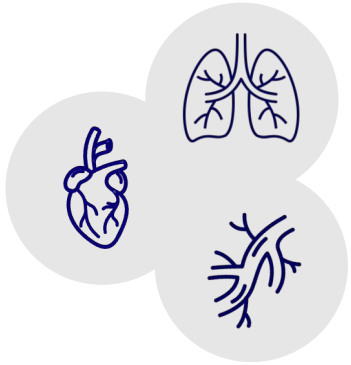
Dr. Deepak Bhatt
Director at Mount Sinai Heart Center, New York City
Dr. Valentin Fuster Professor of Cardiovascular Medicine

Dr. Gunnar Olsson
MD, PhD in Medical Sciences, Karolinska Institute

Dr. Gordon Williams
Prof of Medicine, Harvard Medical School

Dr. Faiez Zannad
Prof of Therapeutics and Cardiology, Université de Lorraine

Promising programs with potential to transform the CVD treatment landscape



Program	Indication	Discovery	Preclinical	Phase I	Phase II	Phase III	Next milestone
CS1	PAH	HDACi with epigenetic effects					Phase II top-line data: Q1, 2023
CS014	CVD	HDACi with epigenetic effects					Phase I H1 2024
CS585	CVD	Prostacyclin receptor agonist					Ongoing preclinical development 2023/2024

HDACi = Histone deacetylase inhibitor

Leaving a mark in the scientific community: Presentations at the top CVD conferences

June 08-11; Frankfurt, Hybrid

CS585 Oral presentation
Abstract Title: Sustained inhibition of platelet activity and thrombosis via iv and oral administration of CS585

- Presented by M. Holinstat

June 24-28; Montreal, CA

CS585 Oral presentation
Abstract Title: CS585 is a novel and highly selective IP receptor agonist for prevention of thrombosis

-Presented by M. Holinstat

July 10-11; Bethesda, US

HDACi presentation
Title: Targeting Histone Deacetylase (HDAC) inhibition for pulmonary hypertension
Participated in a panel discussion.

- Participation by B. Dahlöf R. Benza co-chaired the event

August 25-28; Amsterdam, NL

CS014 & CS585 moderated ePoster

CS014 Abstract Title: HDAC inhibitor CS014 inhibits platelet activity, small and large vessel thrombosis while maintaining hemostasis in a dose-dependent manner

-Presented by M. Holinstat

CS585 Abstract Title: Superiority of CS585 as a selective prostacyclin receptor agonist in prevention of thrombosis

-Presented by L. Stanger (Postdoctoral Research Fellow at UoM)

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Understanding PAH: Debilitating Rare Disease

Dr. Raymond L. Benza
System Director of Pulmonary Hypertension at Mount Sinai Icahn School of Medicine, New York; Chair of Cereno's SAB and PI of Phase II study with CS1

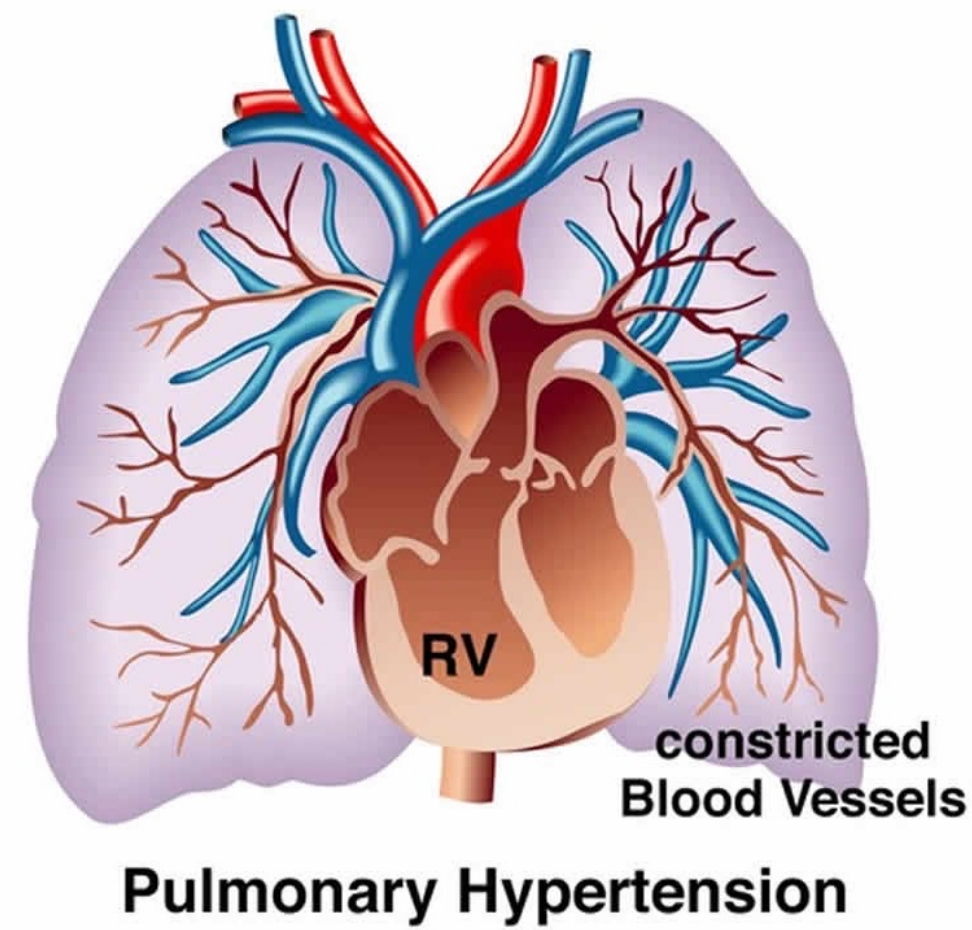
Mount Sinai Heart

Icahn School of Medicine at Mount Sinai

Role of CS1 in Contemporary Treatment for PAH

Raymond L. Benza, MD, FACC, FAHA
Professor of Medicine
System Director Pulmonary Vascular Disease Program
Mount Sinai Heart Institute
Icahn School of Medicine at Mount Sinai
New York, New York USA

PHTN: A Disease of Lung Vessels and the Right Heart but the **Right Heart** determines Prognosis



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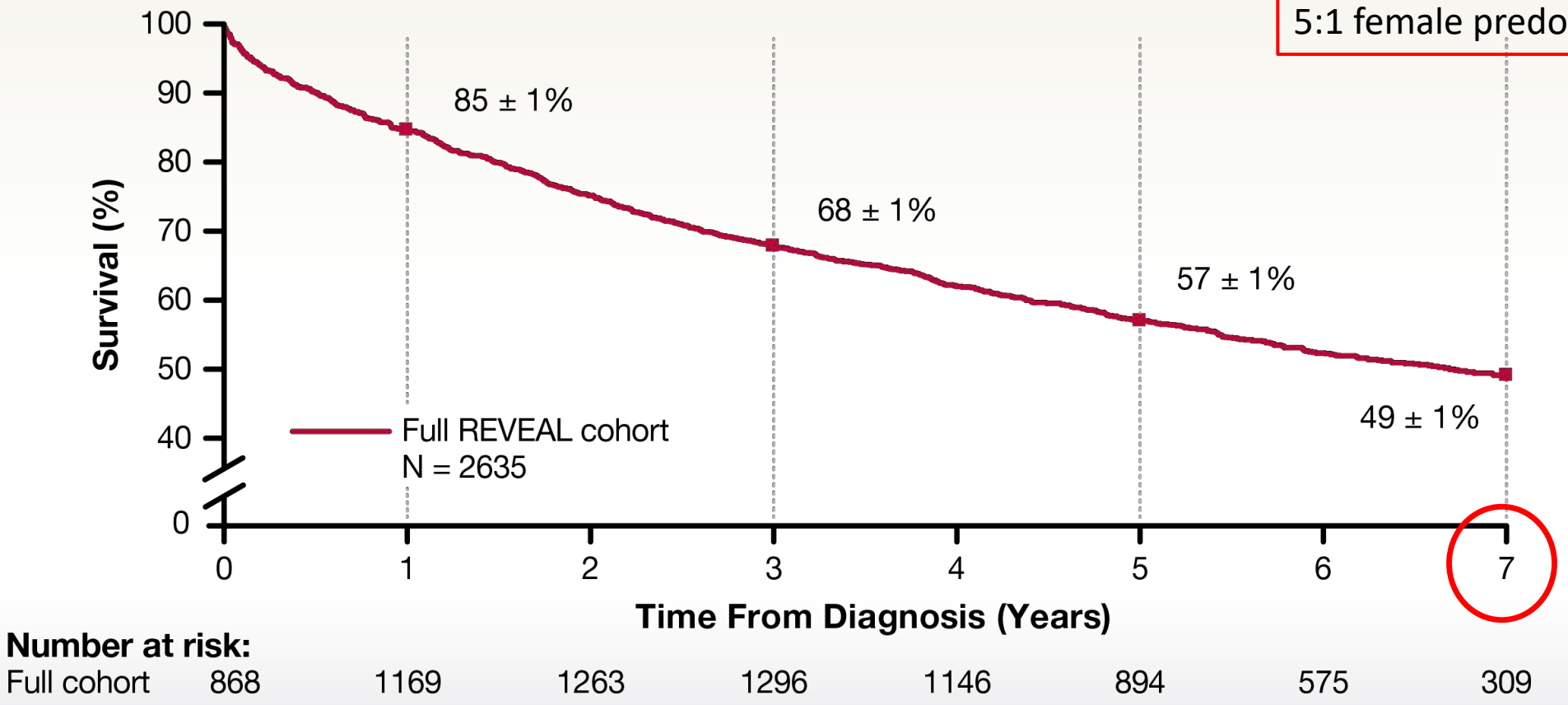
Icahn School of Medicine at Mount Sinai

Seven-Year Survival from Diagnostic RHC on Contemporary Medical Therapy

- W/o Medical therapy, Survival 2.5 years

Mean Age of onset 55yo
5:1 female predominance



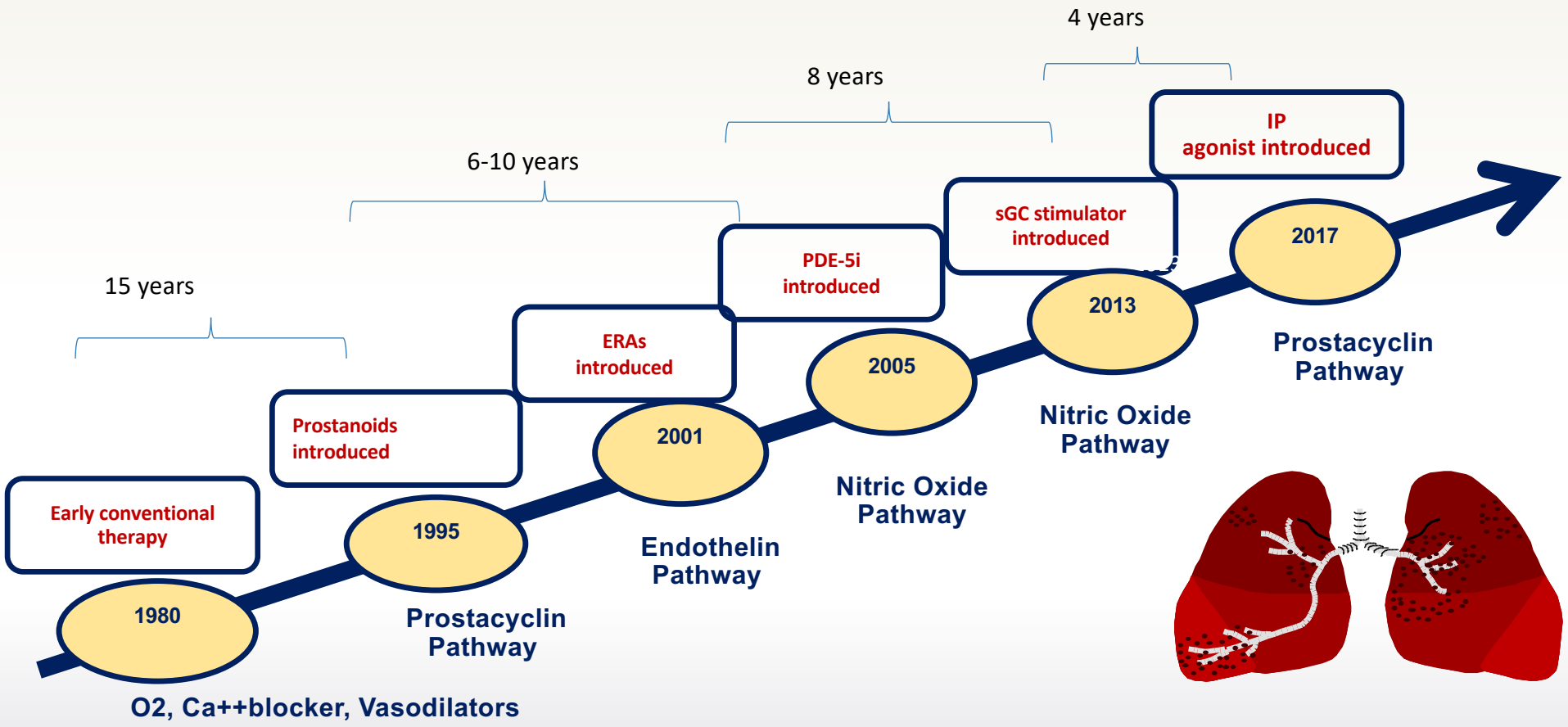
Number at risk:

Full cohort	868	1169	1263	1296	1146	894	575	309

Life expectancy almost tripled

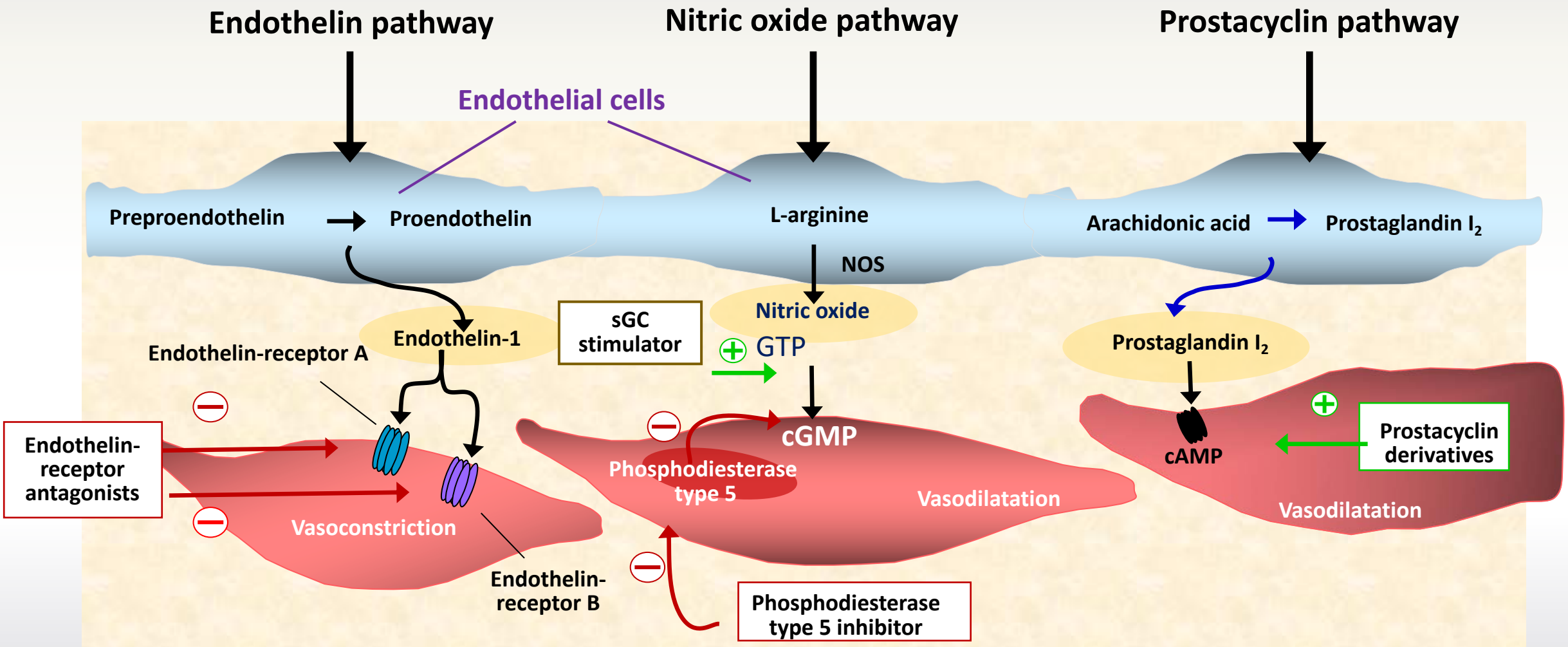
Benza et al., CHEST 2012

PAH Therapeutic Evolution: 1990's to 2020



Agarwal R, Gomberg-Maitland M. *Am Heart J*. 2011;162(2):201-213. Galiè N. *J Am Coll Cardiol.* 2013;62(25 suppl D):D60-D72. Taichman D, et al. *Chest*. 2014;146(2):449-475.

Three Most Cited Mechanisms of PAH



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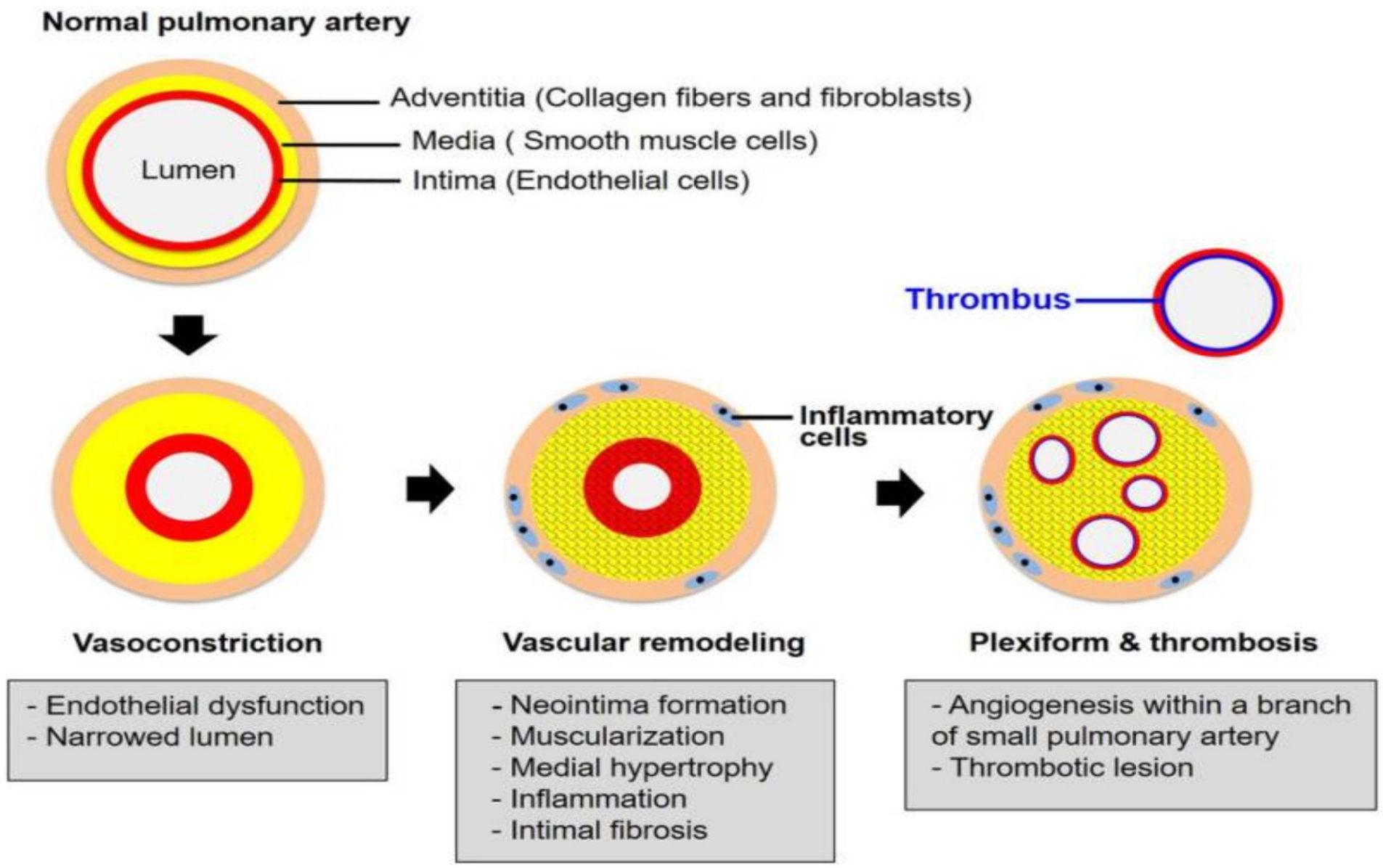
Adapted from: Humbert, et al. *N Engl J Med*. 2004;351:1425-1436.

Icahn School of Medicine at Mount Sinai

Vascular Remodeling in Pulmonary Arterial Remodeling



Woodcock ; J Cardiovasc Pharmacol Ther. 2019 Jul; 24(4): 334–354.

Afterload Lowering Related to Vascular Remodeling to Improve the Right Ventricle: A New Target beyond "Low Risk" for Medical Therapy in Pulmonary Arterial Hypertension?

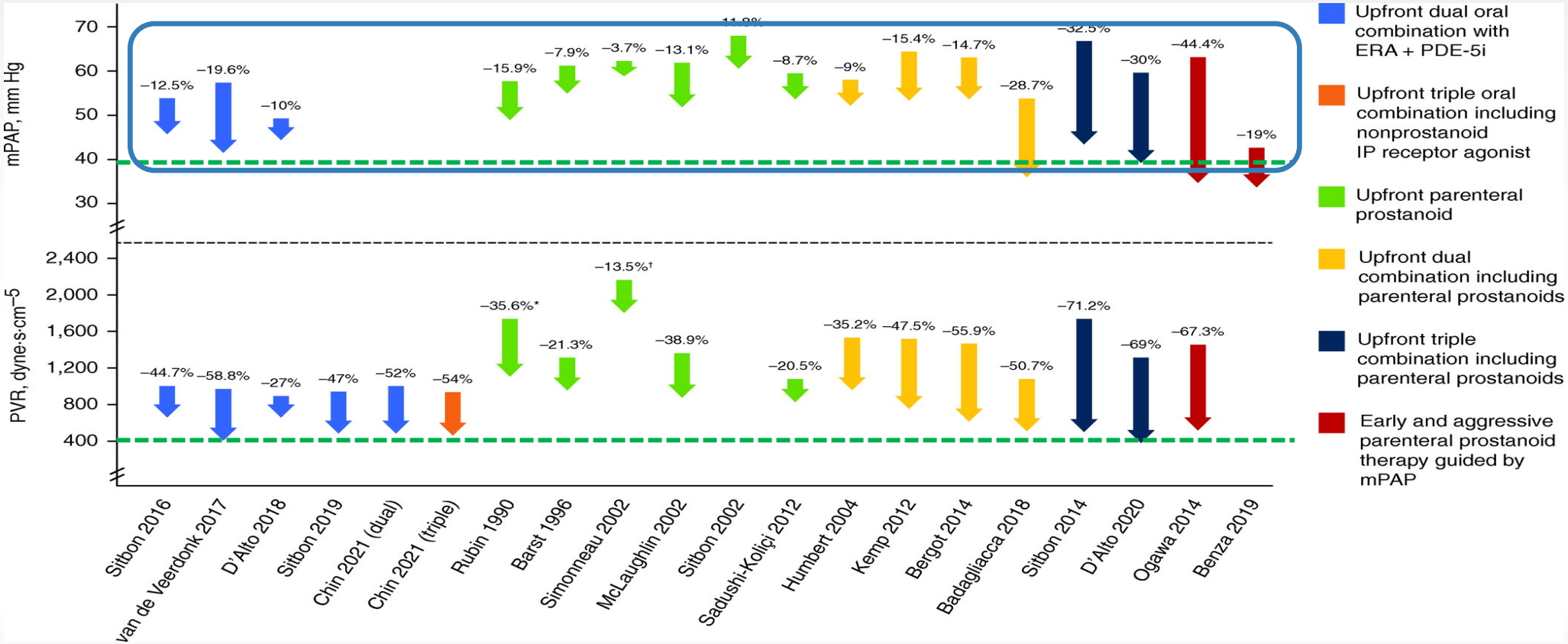
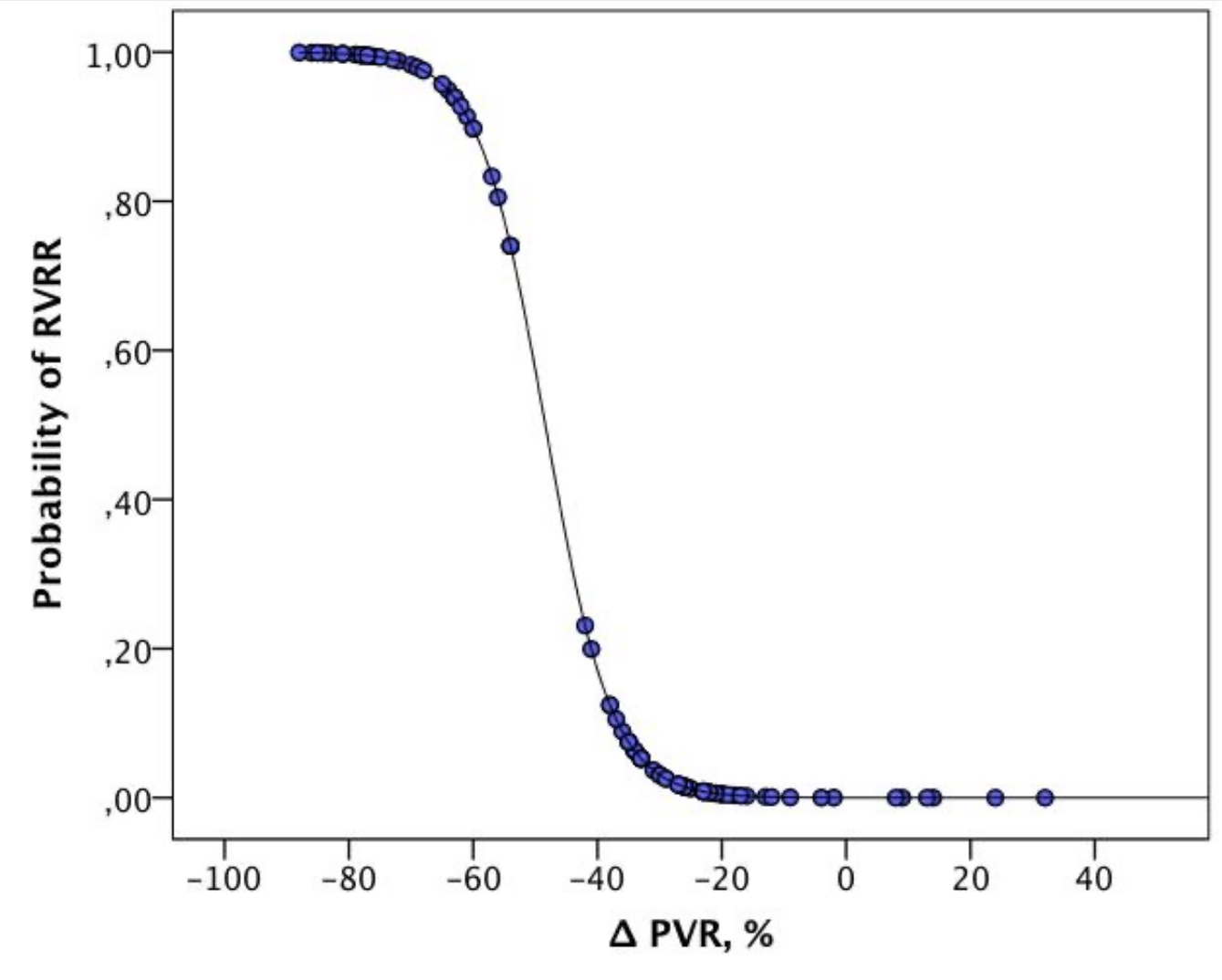


Figure 2. Reductions in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) in the studies cited in the article

Vizza CD, Lang IM, Badagliacca R, Benza RL, Rosenkranz S, White RJ, Matsubara H, et al. Am J Respir Crit Care Med. 2022 Apr 1. 205(7):751-760.

Determinants of RV Reverse Remodeling



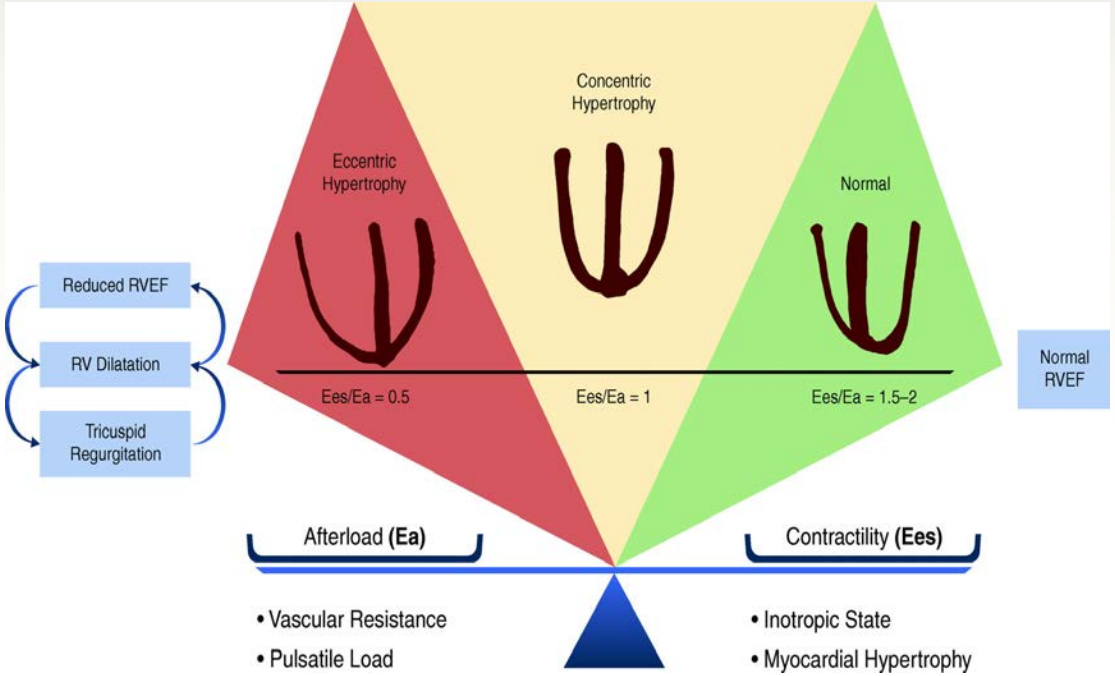
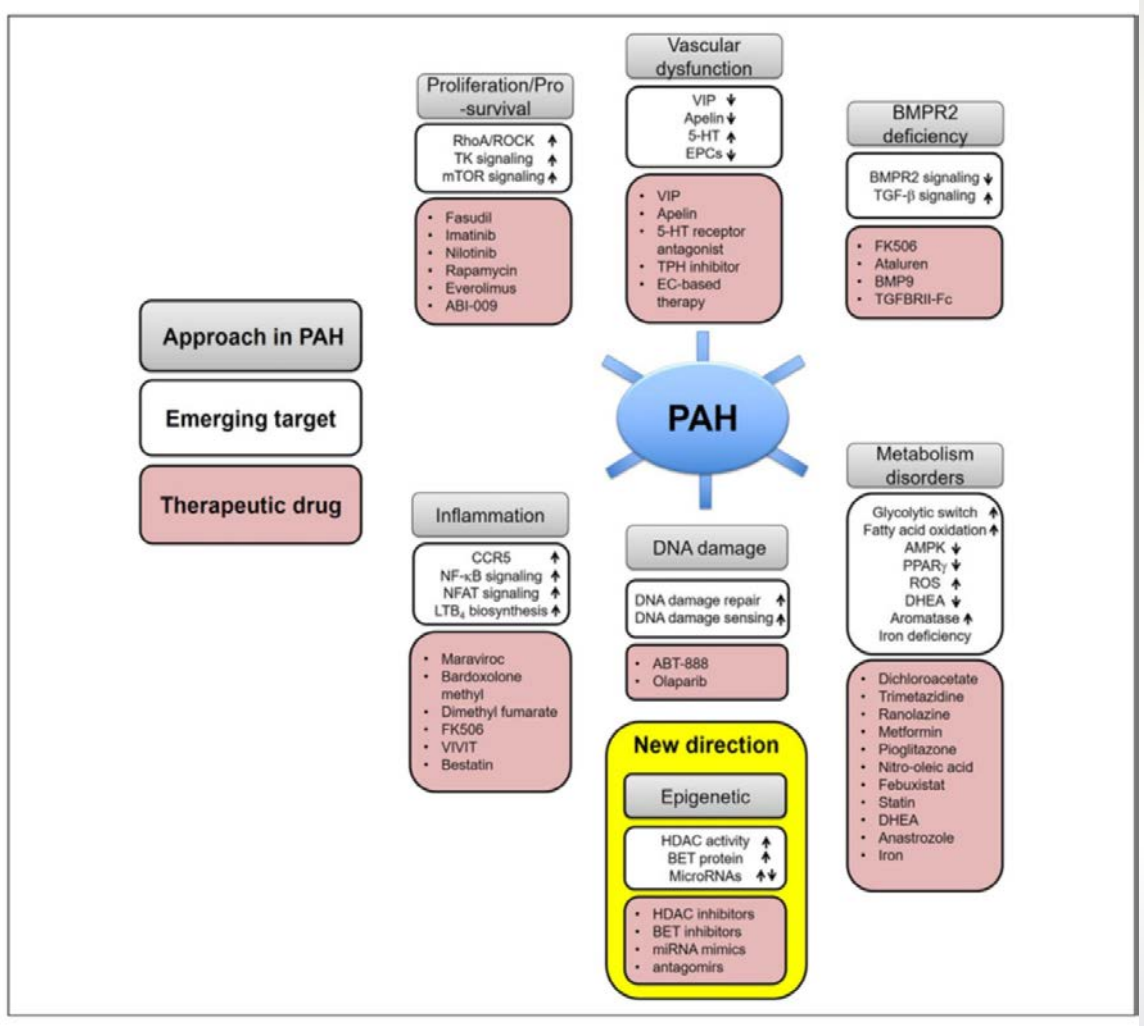


Figure 1. Diagram depicting the interplay among afterload, contractility, and right ventricular (RV) remodeling.

Vizza CD, Badagliacca R, Benza RL, Am J Respir Crit Care Med. 2022 Apr 1. 205(7):751-760.

Badagliacca R, from J Am Coll Cardiol. 2019;73:1463-1482

Push Vascular Remodeling to Normalize mPAP: New Treatment Target for PAH using New Line of Therapeutics



Clinical trials with drugs targeting metabolic dysfunction in pulmonary arterial hypertension

- **Metabolic syndrome: AMPK signalling and metformin**
- **Glycolysis: dichloroacetate**
- **Fatty acid oxidation: ranolazine and trimetazidine**

Clinical trials with drugs targeting inflammation in pulmonary arterial hypertension

- **Modulation of cytokines pathway: anakinra and tocilizumab**
- **Inflammation/Modulation of Nrf2 pathway/NF-κB pathway: bardoxolone methyl, ubenimex, CXA-10**

Clinical trials with drugs targeting other signalling pathways

- **Modulation of the estrogen pathway: anastrozole and fulvestrant**
- **Inhibiting PDGF signaling: Inhaled Iminitab, Seralutinib**
- **Augmenting BMR2 Signaling: Sotatercept**
- **Inhibiting peripheral Serotonin production: Rodatristat**
- **Improvement of oxygenation: acetazolamide**

Sitbon, O Eur Respir J. 2019 Jan; 53(1): 1801908.

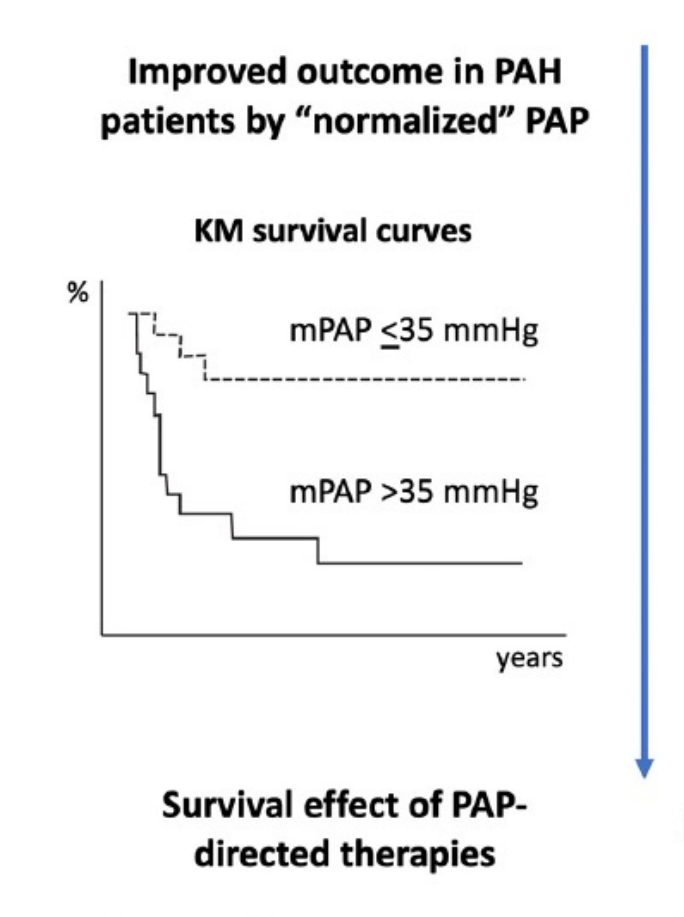
Woodcock ; J Cardiovasc Pharmacol Ther. 2019 Jul; 24(4): 334–354.

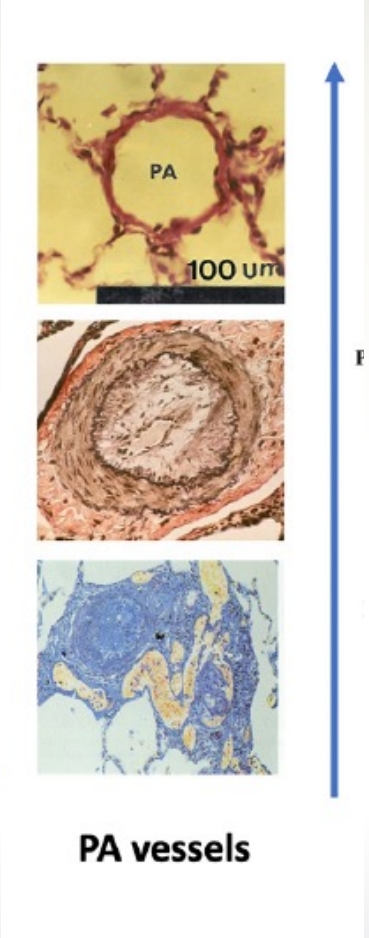
Role of CS1 in PAH Remodeling Treatment Landscape

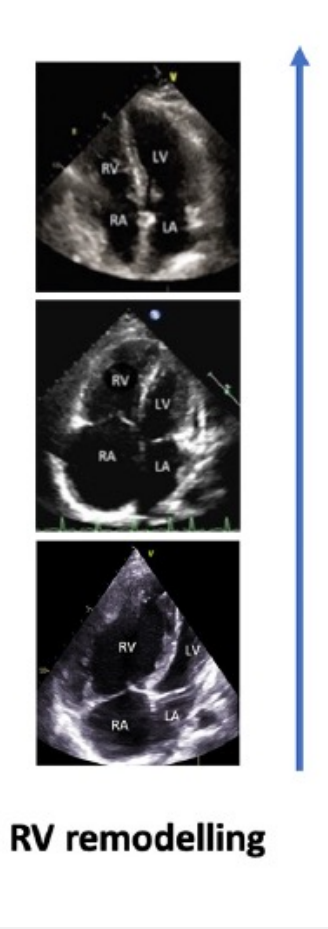
Role of CS1

- Anti-thrombotic activity (restoration of tissue-type plasminogen activator in pulmonary blood vessels and reductin of PAI-1)
- Anti-inflammatory activity
- Anti-fibrotic/remodeling activity
- Pulmonary pressure reduction

Where will CS1 Fit in?







- Prevalent patient to force further remodeling to normalize afterload
- Upfront Therapy with traditional vasodilators
- Primary prevention in High Risk populations (ie scleroderma; multiple PTEs, Genetic variants)
- CTEPH post PEA for residual vasculopathy
- Group 3 disease particularly ILD
- Group 2 Disease (venous remodeling, diastology)

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D'Alto M and Naeije R. Vascul Pharmacol. 2022 Dec; 147: 107124.

Icahn School of Medicine at Mount Sinai

Cereno Scientific

CardioMEMS – Phase II Clinical Collaboration Between Abbott and Cereno

Phil B. Adamson, MD, MSc
Divisional Vice President and Chief Medical Officer Heart Failure Division, Abbott

CERENO SCIENTIFIC – ABBOTT COLLABORATION

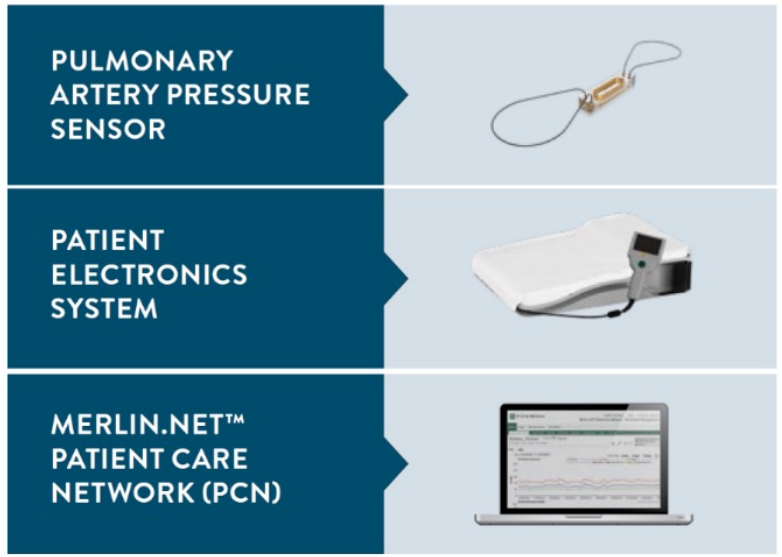
CardioMEMS HF System™

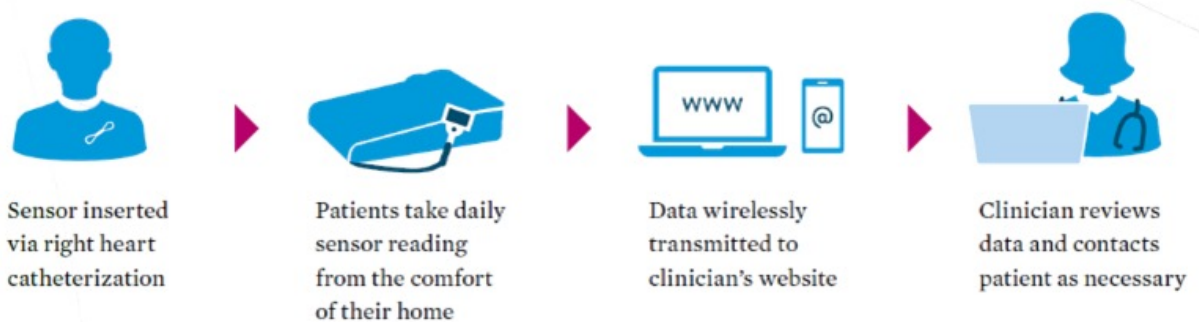
CS1 in pulmonary arterial hypertension

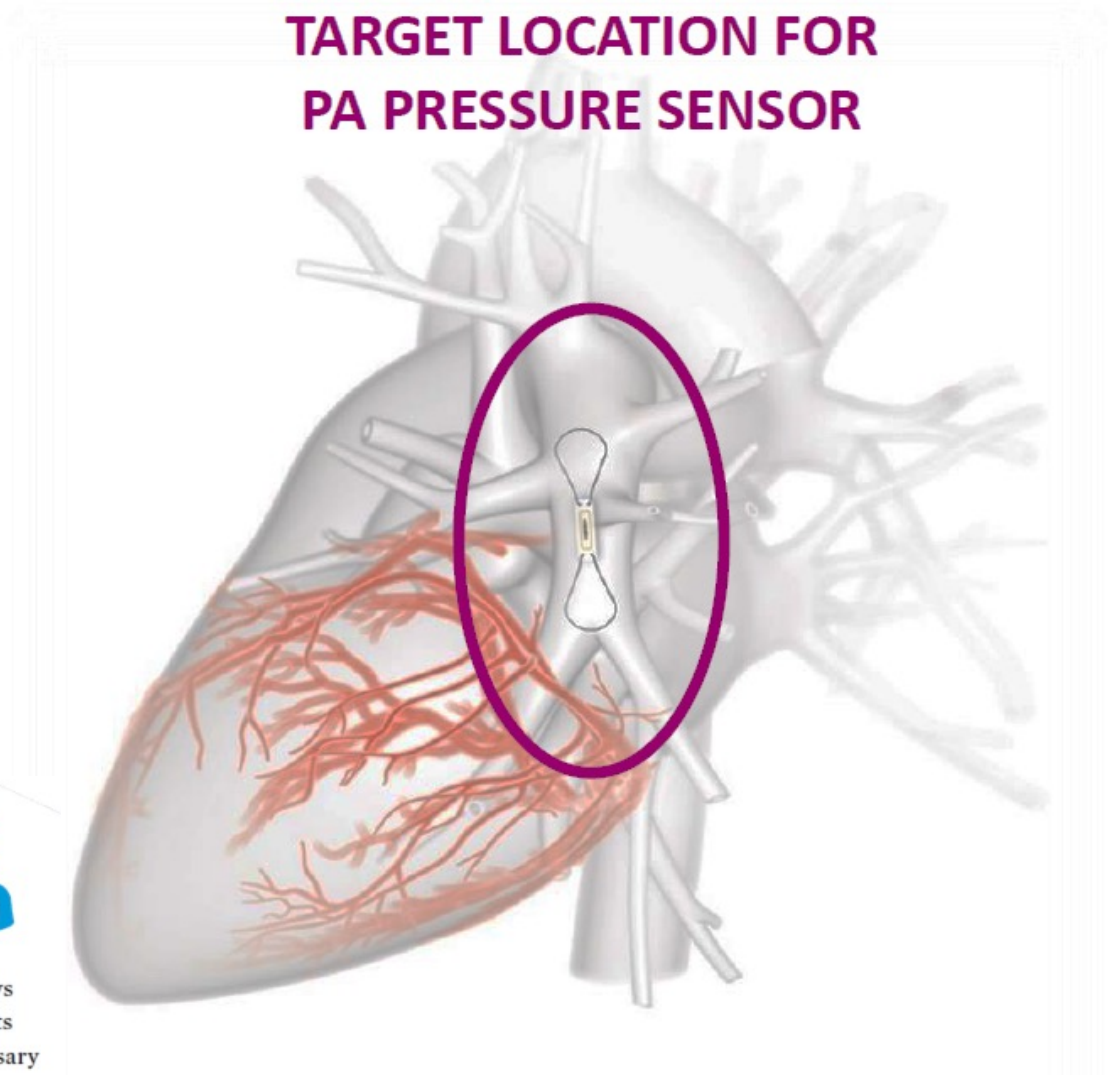
30 August 2023

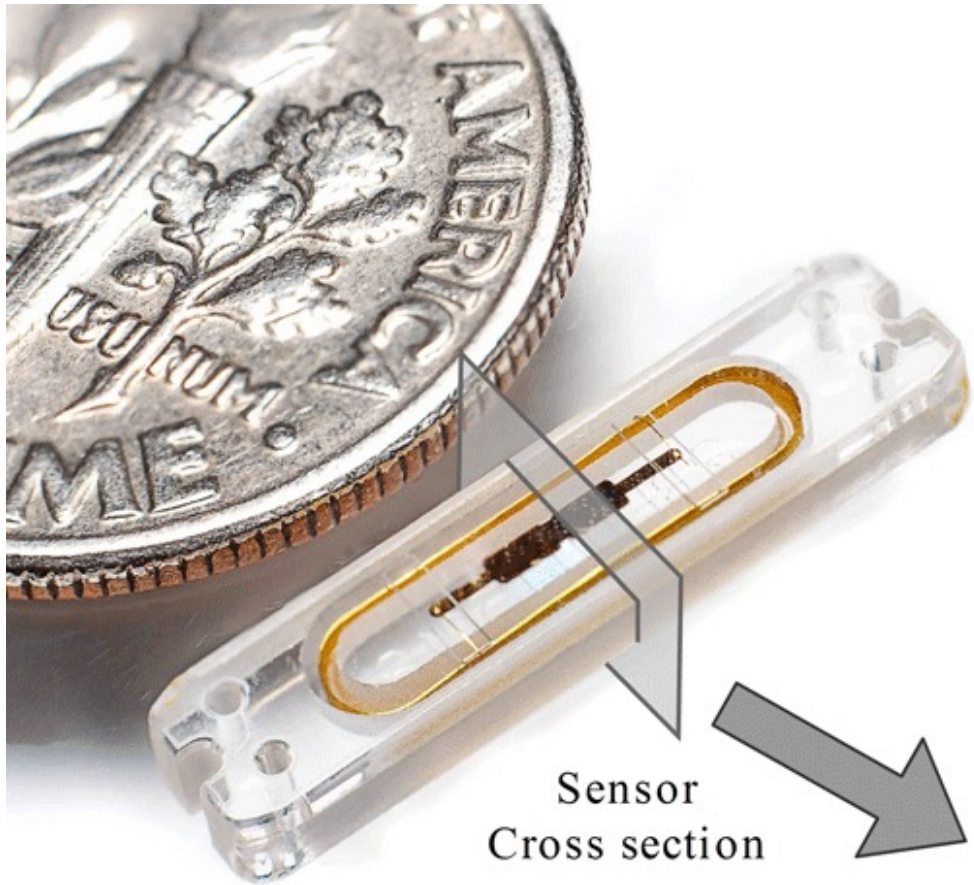
Philip B. Adamson, MD, MSc, FACC, FESC, FRCP (Ed)
Divisional Vice President, Chief Medical Officer
Abbott Heart Failure Division

CardioMEMS HF Monitoring System









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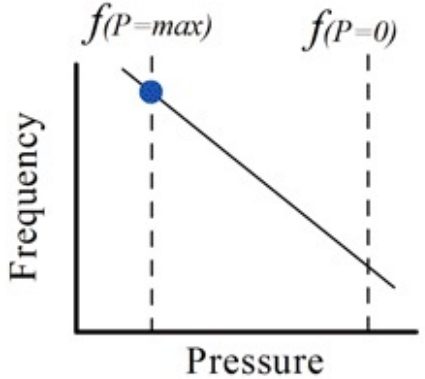
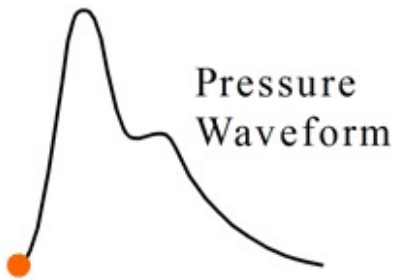
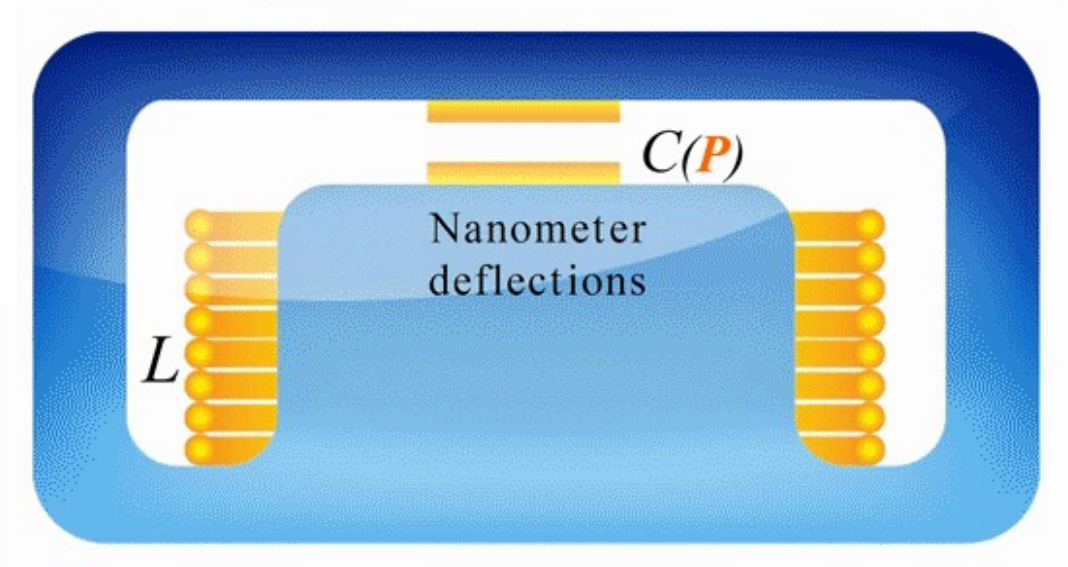
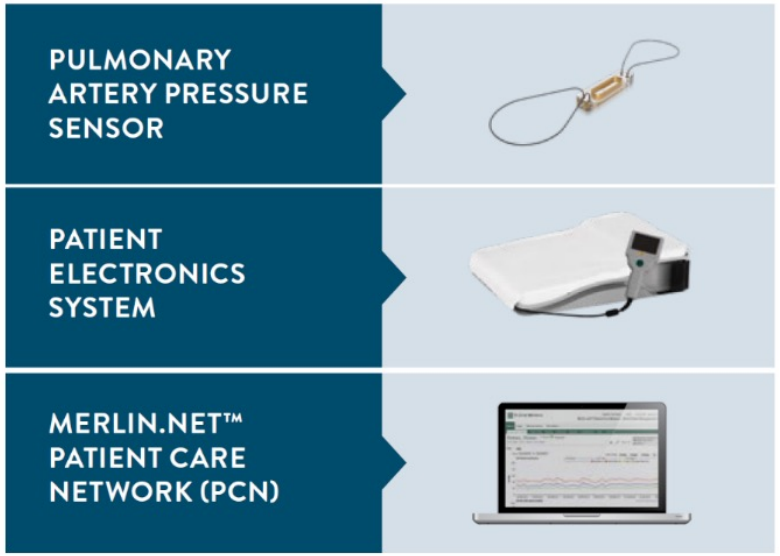
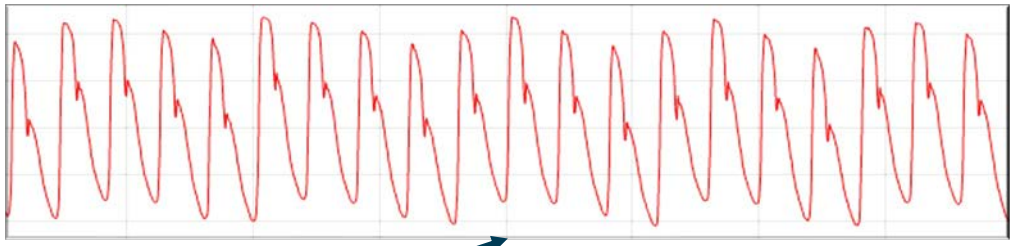






CardioMEMS HF Monitoring System





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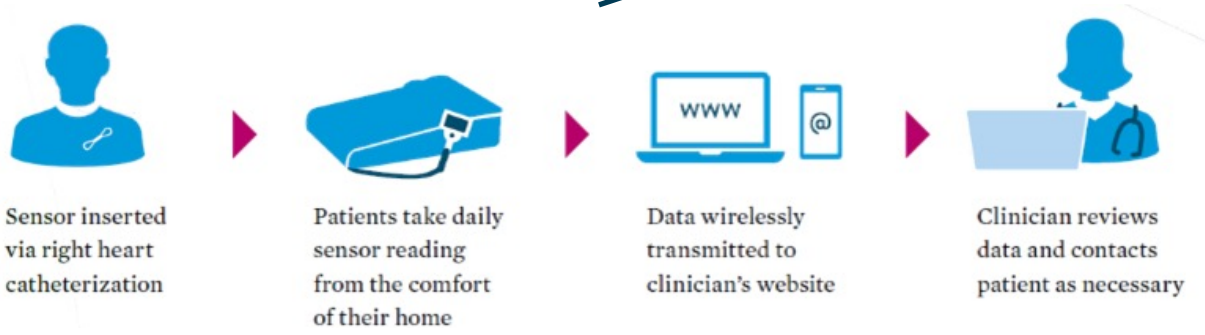
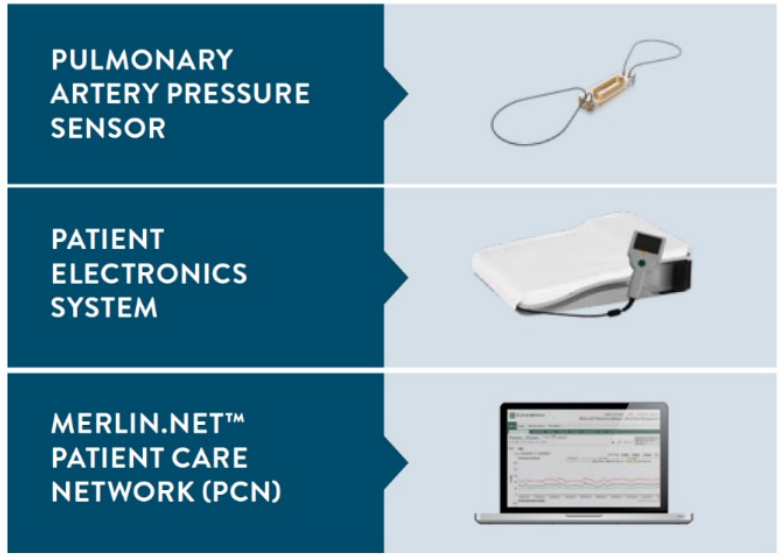
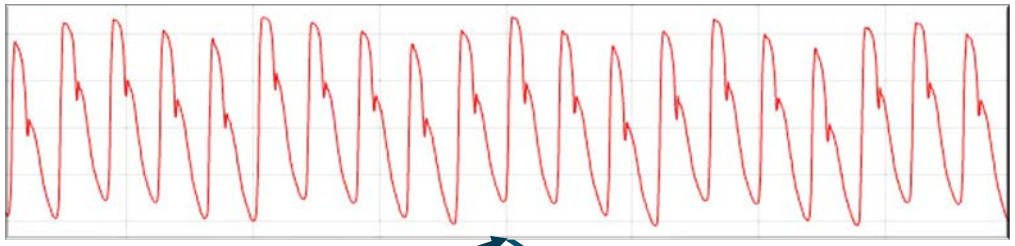


CardioMEMS HF Monitoring System





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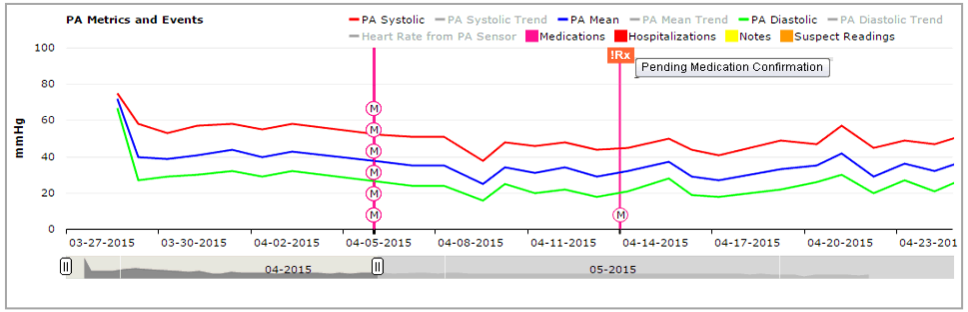
PA SYSTOLIC, DIASTOLIC AND MEAN. HEART RATE

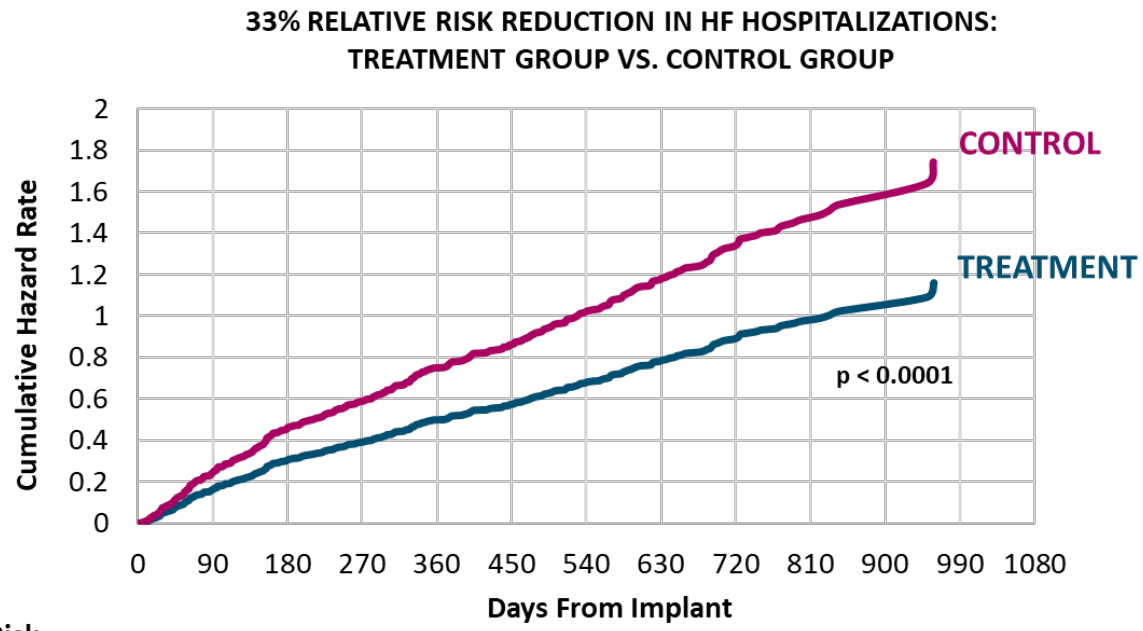


CHAMPION Randomized Clinical Trial:

PRIMARY EFFICACY ENDPOINT MET WITH SIGNIFICANTLY REDUCED HF HOSPITALIZATION

- Pulmonary Artery Pressure
- Medication Changes Based on Pulmonary Artery Pressure ($p < 0.0001$)
- Pulmonary Artery Pressure Reduction ($p = 0.008$)
- Reduction in Heart Failure Hospitalizations ($p < 0.0001$)
- Quality of Life Improvement ($p = 0.024$)

PART 1: RANDOMIZED ACCESS



CURRENT INDICATION: NYHA Class III HF subjects with a HF hospitalization within the prior 12 months

1. Abraham WT, et al. *Lancet*, 2011.
2. Abraham WT, et al. *Lancet*, 2016.

Totality Of Evidence: PA Pressure Guided Care

Study Type	Study	N	Follow-up	Reduction in HFH	p-value
RCT	GUIDE-HF IDE [1]	946	8.6 mo.	32%	p < 0.01
RCT	CHAMPION IDE [2]	550	18 mo.	33%	p < 0.0001
RCT	Monitor-HF[3]	348	12 mo.	44%	P < 0.005
RCT	PASSPORT-HF	554	12 mo.	Ongoing	
Meta-analysis	Patient level 3-RCT outcomes	1,350	24 mo.	36% HFH 25% Mort	
Retrospective	Propensity Matched Outcomes [4]	2,174	12 mo.	24%	p < 0.001
Single Arm	US Post-approval Study [5,6]	1,200	24 mo.	57%	p < 0.0001
Single Arm	MEMS-HF European Study [7]	234	12 mo.	62%	p < 0.0001
Single Arm	COAST-UK Registry [8] (NICE Guidance)	100	12 mo.	82%	p < 0.0001
Retrospective	Real World Clinical Practice: Claims Analysis [9,10]	1114 480	6 mo. 12 mo.	45% 34%	p < 0.001 p < 0.001

1. Lindenfeld, J., 2021, *Lancet (*NYHA Class II/III pre-COVID 19 follow-up cohort)
2. Abraham, W. , 2011 and 2016, *Lancet* (18mo. median follow-up)
3. Brugts JJ, *Lancet* 2023
4. Abraham, J., 2019, *JAMA*
5. Shavelle, D., 2020, *Circulation: HF*
6. Heywood JT et al. J Card Fail 2023;29:56-66.
7. Angermann C, et al. *Eur J Heart Fail.* 2020.
8. Cowie, M., 2021, ESC HF
9. Desai, A., 2017, *JACC*
10. Heywood J., 2017, *Circulation*

Articles

Remote haemodynamic monitoring of pulmonary artery pressures in patients with chronic heart failure (MONITOR-HF): a randomised clinical trial

Jasper J Brugts, Sumant P Radhoe*, Pascal R D Clephas†, Dilan Aydin†, Marco W F van Gent, Mariusz K Szymanski, Michiel Rienstra, Mieke H van den Heuvel, Carlos A da Fonseca, Gerard C M Linssen, C Jan Willem Borleffs, Eric Boersma, Folkert W Asselbergs, Arend Mosterd, Hans-Peter Brunner-La Rocca, Rudolf A de Boer for the MONITOR-HF investigators*

www.thelancet.com **Published online May 20, 2023** https://doi.org/10.1016/S0140-6736(23)00923-6

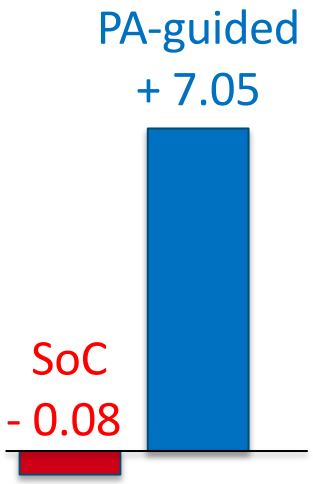
Monitor-HF

The third prospective RCT demonstrating benefit of CardioMEMS guided care

Primary Outcome; Health Assessment (KCCQ-OS)

Mean KCCQ-OS (SD)	PA-guided	SoC	P-value
- Baseline (n=348)	55.8 (23)	54.9 (22)	0.69
- 12 months (n=279)	66.1 (25)	56.9 (24)	0.01

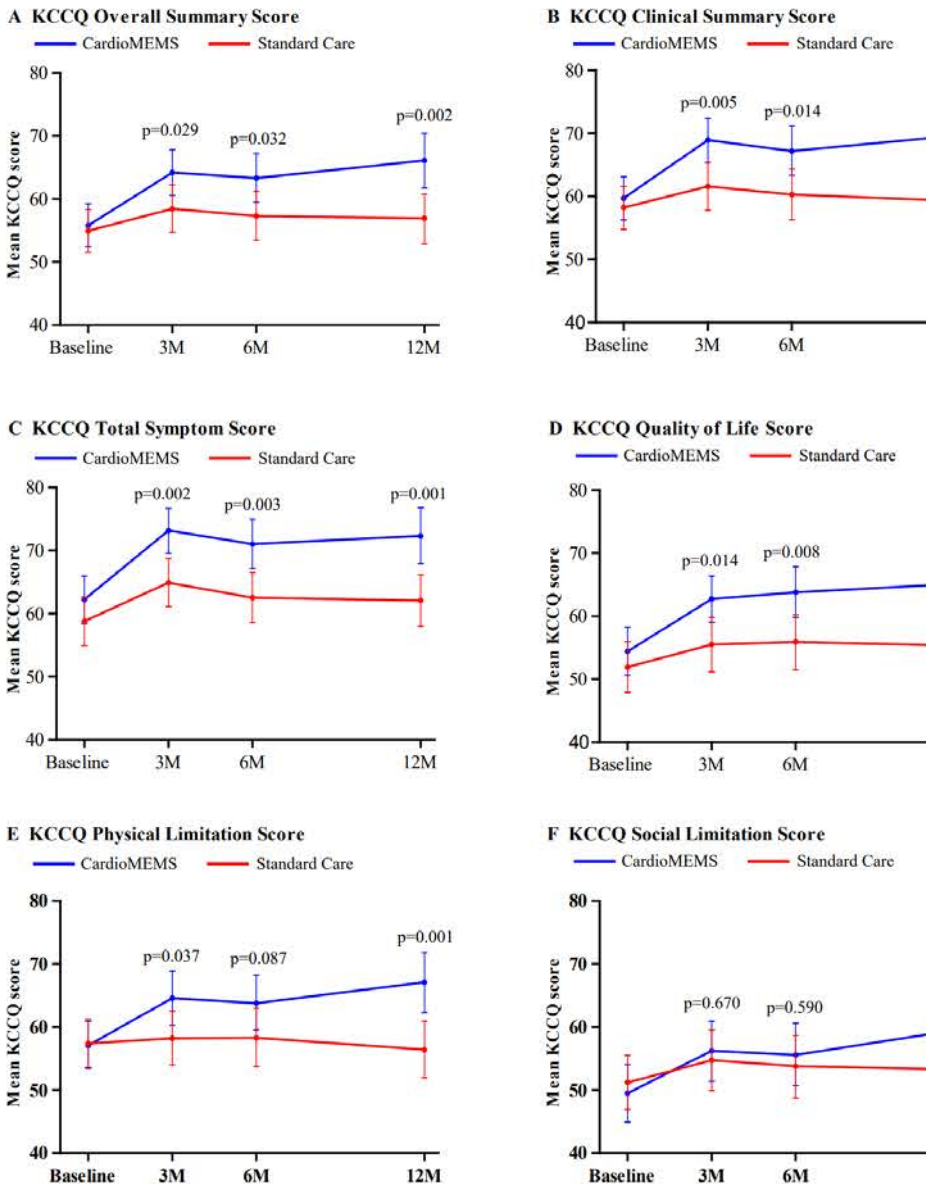
Mean difference baseline to 12M between groups



+ 7.13 (95% CI 1.5-12.8)
P=0.013

Sensitivity analyses for missing data yielded similar results

KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score

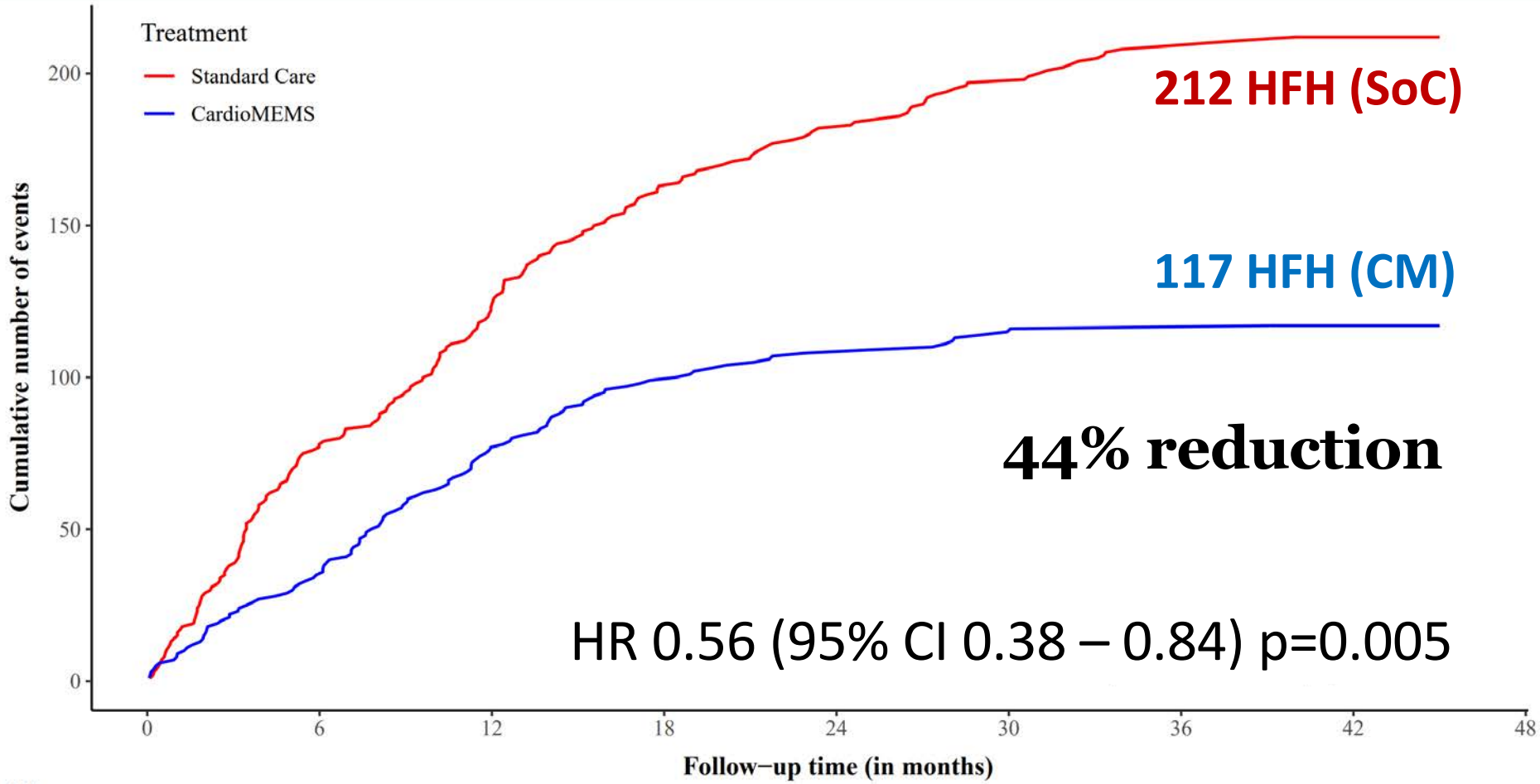


Brugts JJ et al Lancet 2023; https://doi.org/10.1016/S0140-6736(23)00923-6

Reduction In Number Of Total HF Hospitalisations

Cox-regression analysis
Andersen-gill method
(Recurrent events)

Mean follow-up:
1.8 years (SD 0.9)



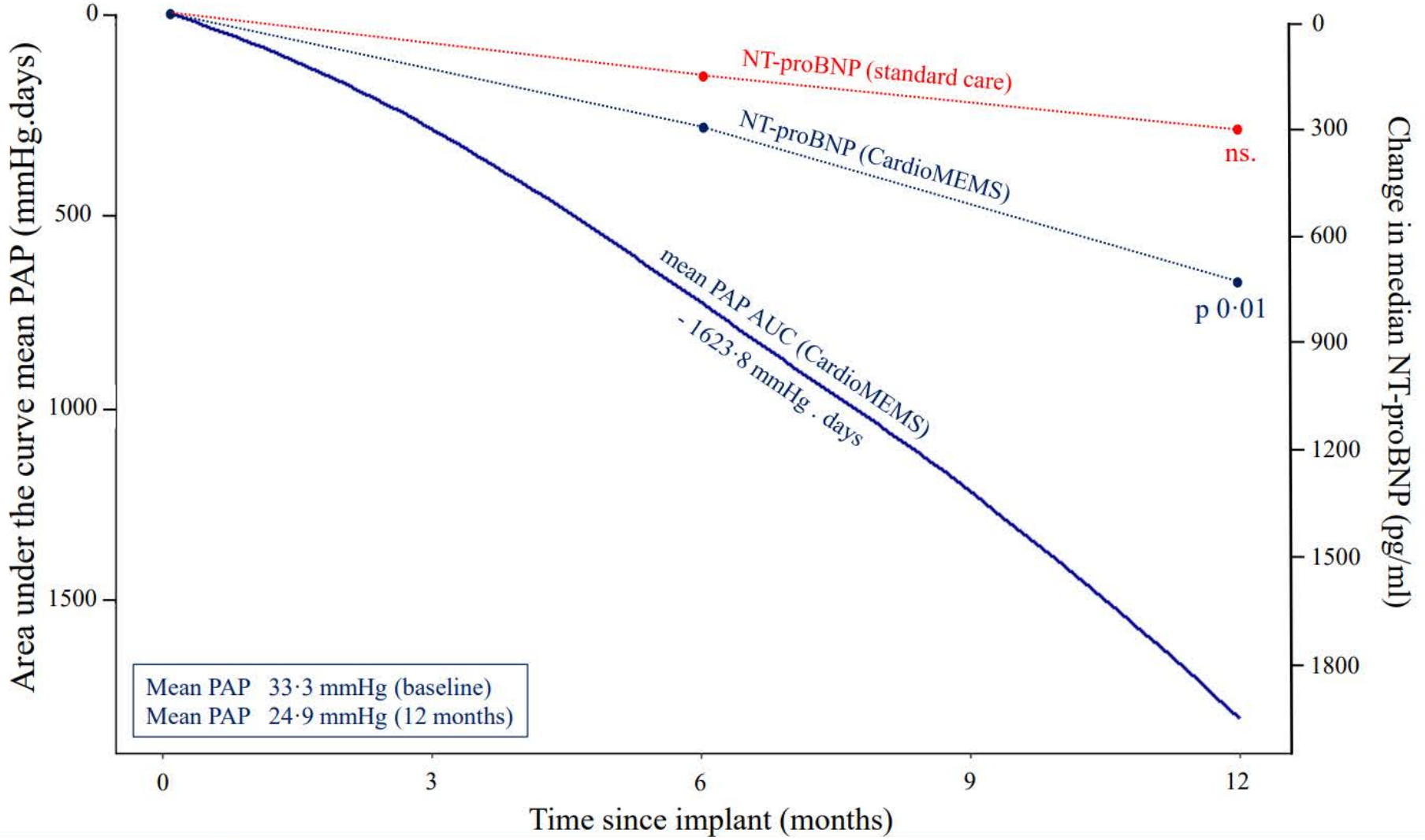
Number at risk									
CardioMEMS	176	159	130	93	66	41	20	7	0
Standard Care	172	160	147	102	67	40	22	2	0

Brugts JJ et al Lancet 2023; https://doi.org/10.1016/S0140-6736(23)00923-6

Effect Of The Intervention At Multiple Levels

- Strong reduction in mean PA pressure

- Significant reduction in NT-proBNP only in PA-guided group

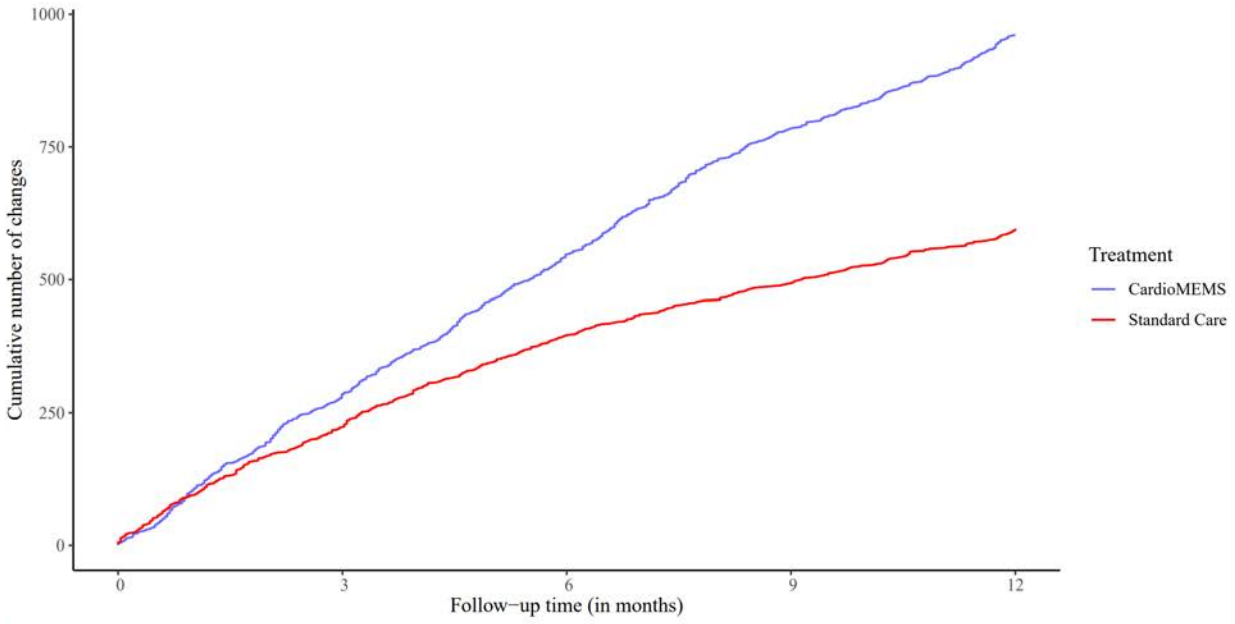


Brugts JJ et al Lancet 2023; https://doi.org/10.1016/S0140-6736(23)00923-6

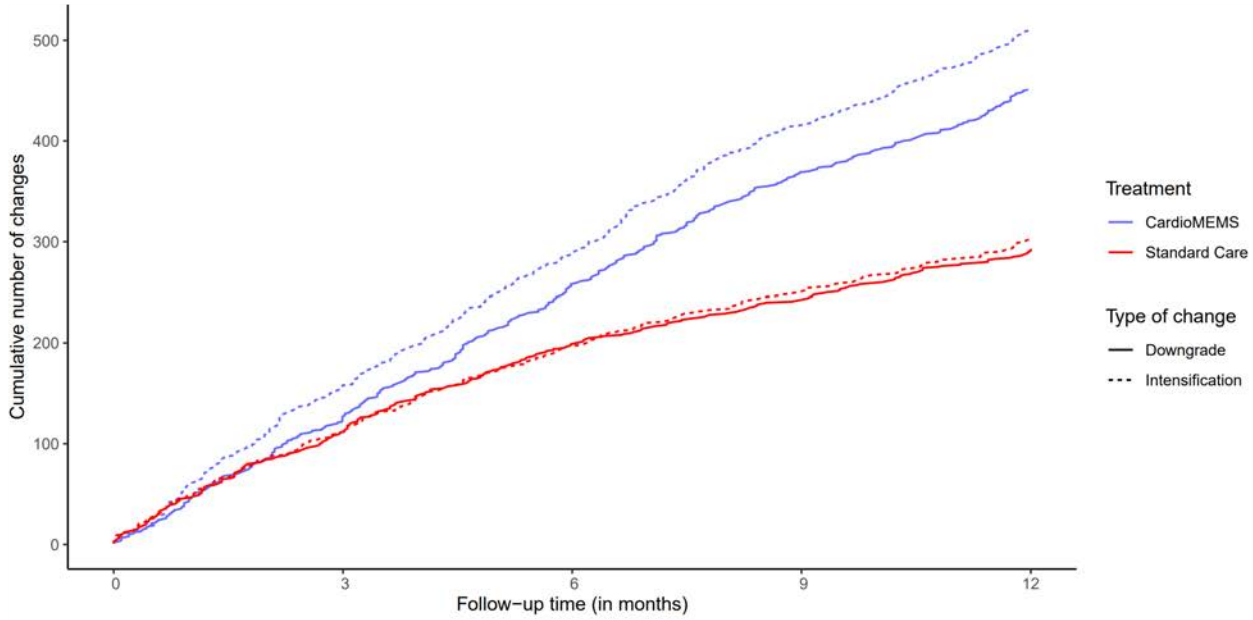
Mode Of Effect: Pressure Guided Medication Titration

Remote personalization of medical therapies – titrate to effect

A. Cumulative changes in diuretics



B. Type of changes in diuretics: fine-tuning



Brugts JJ et al Lancet 2023; https://doi.org/10.1016/S0140-6736(23)00923-6

GUIDE-HF Demonstrated Safety of Device and Implant

STRONG SAFETY PROFILE OF CARDIOMEMS CONSISTENT ACROSS TRIALS

- GUIDE-HF demonstrated a **99.2% freedom from device or system-related complications**
- The occurrence of device or system-related complications has remained low across all CardioMEMS trials to date

DEVICE OR SYSTEM-RELATED COMPLICATIONS

Trial	Patients	Events (%)
GUIDE-HF	**1022**	**8 (0.8%)**
CHAMPION	575	8 (1.4%)
US PAS	1,214	4 (0.3%)
MEMS-HF	236	4 (1.7%)
Totals	3,047	24 (0.8%)

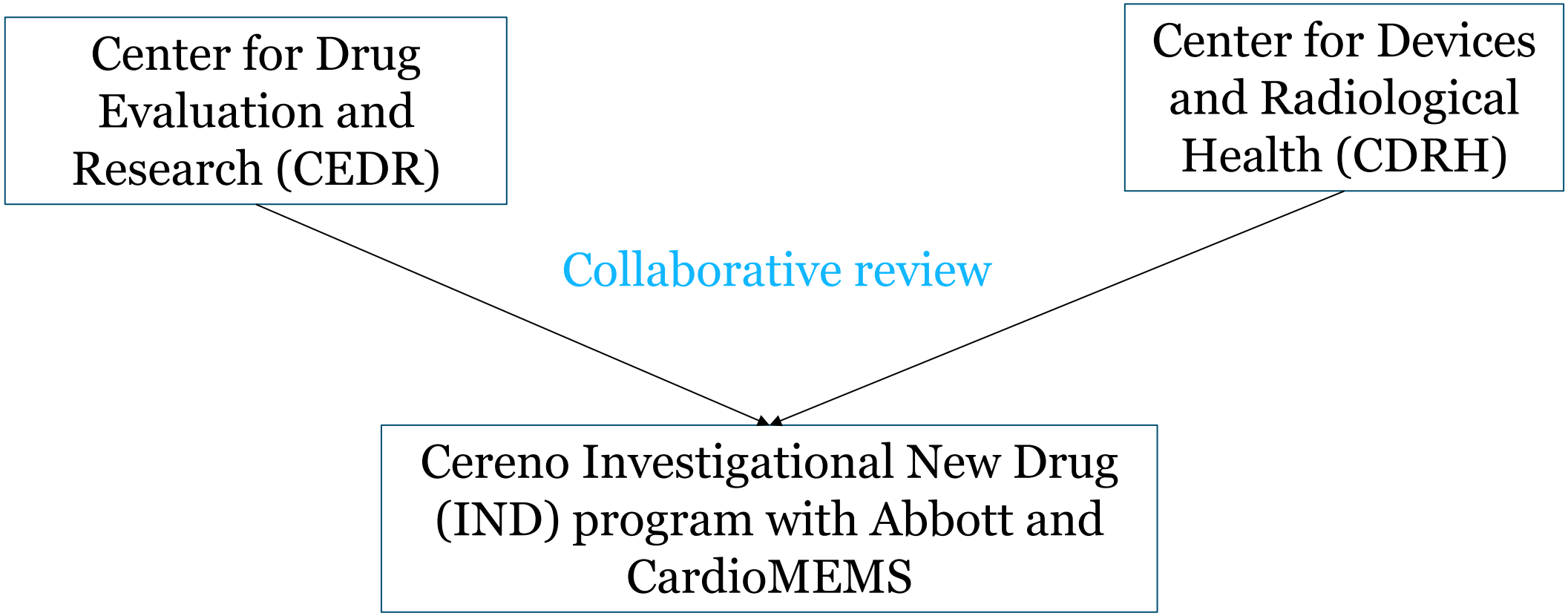
Current USFDA and CE Mark approved CardioMEMS indications

February 21, 2022

US	The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in NYHA Class II or III heart failure patients who either have been hospitalized for heart failure in the previous year and/or have elevated natriuretic peptides. The hemodynamic data are used by physicians for heart failure management with the goal of controlling pulmonary artery pressures and reducing heart failure hospitalizations.
CE	The CardioMEMS™ HF System is indicated for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in NYHA Class III heart failure patients with a hospitalization in the prior 12 months. Hemodynamic data are used with the goal of reducing heart failure hospitalizations

Cereno – Abbott Collaboration

US Food and Drug Administration



life. to the fullest.®

Abbott

Thank you!

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Cereno's CS1: Clinical Phase II Study Design

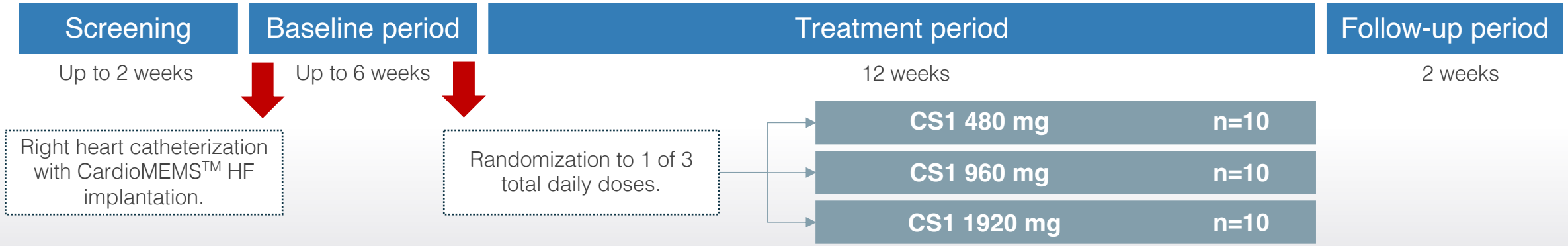
Dr. Raymond L. Benza

System Director of Pulmonary Hypertension at Mount Sinai Icahn School of Medicine, New York City; Chair of Cereno's SAB and PI of Phase II study with CS1

CS1 Phase II study aims to evaluate safety, tolerability and exploratory efficacy

Phase II study of CS1 in patients with PAH

- Primary endpoint: Safety and tolerability.
- Other variables including all standard efficacy endpoints for this patient group (6MWT etc.), a calculated validated risk score, pharmacokinetics, and dose-finding based on mPAP changes.
- Abbott's CardioMEMS™ HF System technology for monitoring pulmonary pressure and pulmonary/RH hemodynamics.
- Includes 30 patients, at 10 different US clinical sites.
- Expected top-line results: Q1 2023.



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Phase 2 Study of CS1 in Subjects with Pulmonary Arterial Hypertension

- Novel Compound with Novel Actions
- Novel and Innovative Endpoints
  - REVEAL Risk Score
  - Cardiac MRI
  - CardioMEMs device
  - Novel biomarkers
- Traditional Endpoints (efficacy and safety)
  - 6MWD, hemodynamics, echo, biomarker

REVEAL 2.0 and REVEAL Lite 2: Risk Score Calculators

REVEAL 2.0 Risk Calculator

Print | Reset

Select all variables that apply. A minimum of 7 variables are required to generate a score. Calculation accuracy increases with more selections.

					Score
WHO Group 1 Subgroup	CTD-PAH 1	Heritable 2	PoPH 3	Other 0	–
Demographics - Male age > 60 years		No 0	Yes 2		–
eGFR<60mL/min/1.73m² or renal insufficiency		No 0	Yes 1		–
NYHA/WHO Functional Class	I -1	II 0	III 1	IV 2	–
Systolic BP (mm Hg)		SBP≥110 0	SBP<110 1		–
Heart Rate (BPM)		HR≤96 0	HR>96 1		–
All-Cause Hospitalizations ≤ 6 mo		No 0	Yes 1		–
6-Minute Walk Test (m)	≥440 -2	320 to 440 -1	<320 to 165 0	<165 1	–
BNP (pg/mL)	50 -2	50 to <200 0	200 to <800 1	≥800 2	–
or					
NT-proBNP (pg/mL)	<300 -2	300 to <1100 0	≥1100 2		–
Pericardial Effusion on Echocardiogram		No 0	Yes 1		–
% predicted DL_{CO} ≤40		No 0	Yes 1		–
mRAP >20 mm Hg Within 1 Year		No 0	Yes 1		–
PVR < 5 Wood units on right heart catheterization		No 0	Yes -1		–
					+6
				Risk score	--

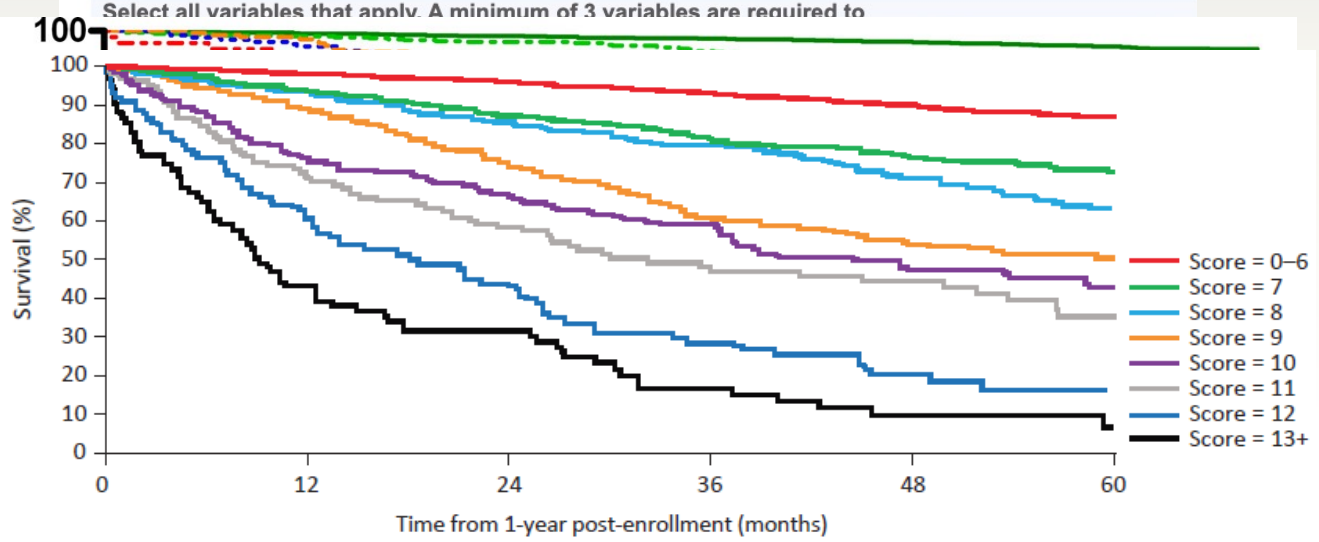
12 Variables

	Low risk	Intermediate risk	High risk
Risk score	0-6	7-8	≥9

REVEAL Lite 2 Risk Calculator

Print | Reset

Select all variables that apply. A minimum of 3 variables are required to



Number at risk

Score = 0–6	1073	1032	961	839	743	343
Score = 7	386	344	304	257	217	114
Score = 8	306	275	236	194	155	79
Score = 9	266	230	178	133	100	46
Score = 10	195	142	116	88	58	32
Score = 11	130	87	67	40	30	13
Score = 12	90	54	34	21	11	5
Score = 13+	83	34	24	10	5	2

	Low risk	Intermediate risk	High risk
Risk score	≤5	6-7	≥8

REVEAL is capable of offering >12 lines of risk: offering better granularity and discrimination at all levels of risk

Benza R: Chest. 2019 Aug;156(2):323-337; Benza RL Chest. 2021 Jan;159(1):337-346; Rich JD, J Am Heart Assoc. 2018 Oct 16;7(20):e009594.

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REVEAL 2.0 and REVEAL Lite 2 Allow % Prediction in Outcome after Quantitative Changes in Continuous Scores.

- **Freedom EV: For REVEAL 2.0 a 1 point decrease in score at Week 12 predicted a 62% decrease in the relative risk of CW (hazard ratio (HR) 0.38, CI 0.32, 0.45, *p* < .001).**
- **Freedom EV: For REVEAL Lite 2, a 1 point decrease in score at Week 12 predicted a 59% decrease in the relative risk of CW (HR 0.41, CI 0.34, 0.48, *p* < .001).**
- **Griphon: For REVEAL Lite 2 For every 1-point decrease in REVEAL Lite 2 risk score, MME risk decreased by 45% (P<0.0001)**
    - For every 1-point increase in risk score from baseline, MME risk increased by 68% (P<0.0001)
- **PATENT: For REVEAL 2.0 for every a 1-point improvement in RRS 2.0 was associated with a 26% reduction in the relative risk of death and a 23% reduction in the relative risk of clinical worsening**

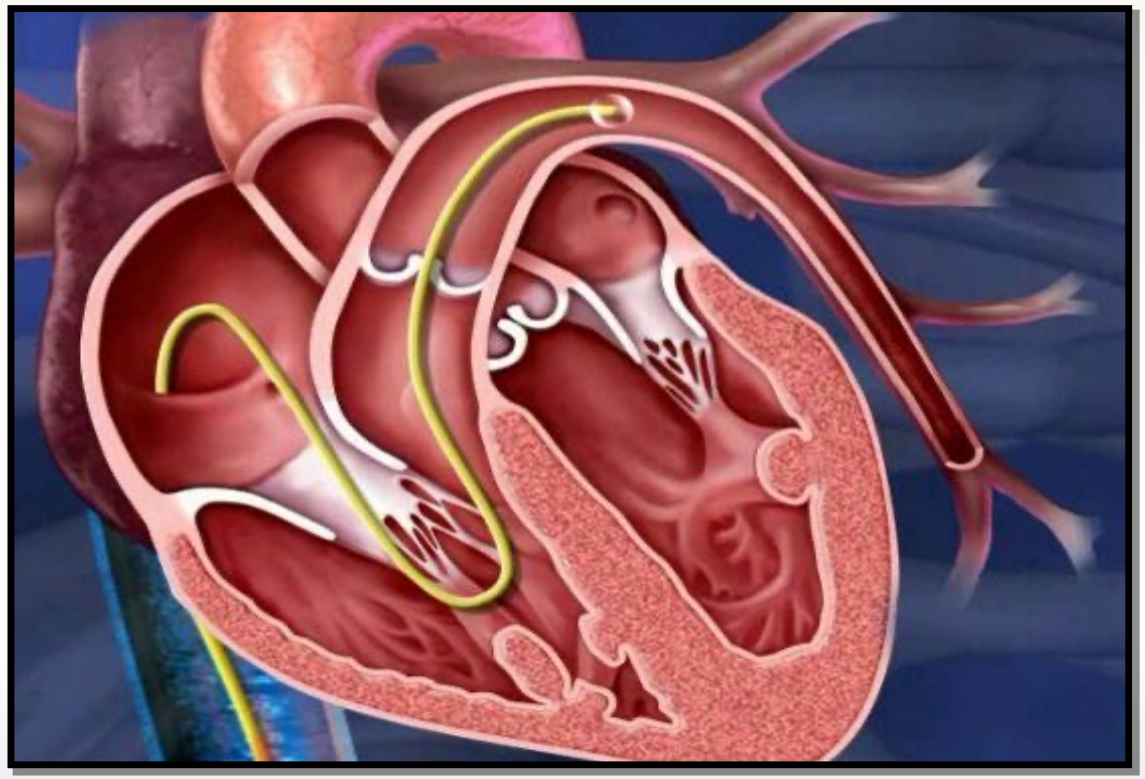
Benza R, JHLT 2022 (41) 11, 1572-1580, Benza R, JHLT 2022 (41) 3, 411-420; Benza RIJCard 2021 (33) 189-192; Benza R CHEST 2021

Right Heart Catheterization: Contemporary Gold Standard for Evaluating PAH & RV Function

Hemodynamics are the Most Important Piece of HF Management but not Readily Obtainable

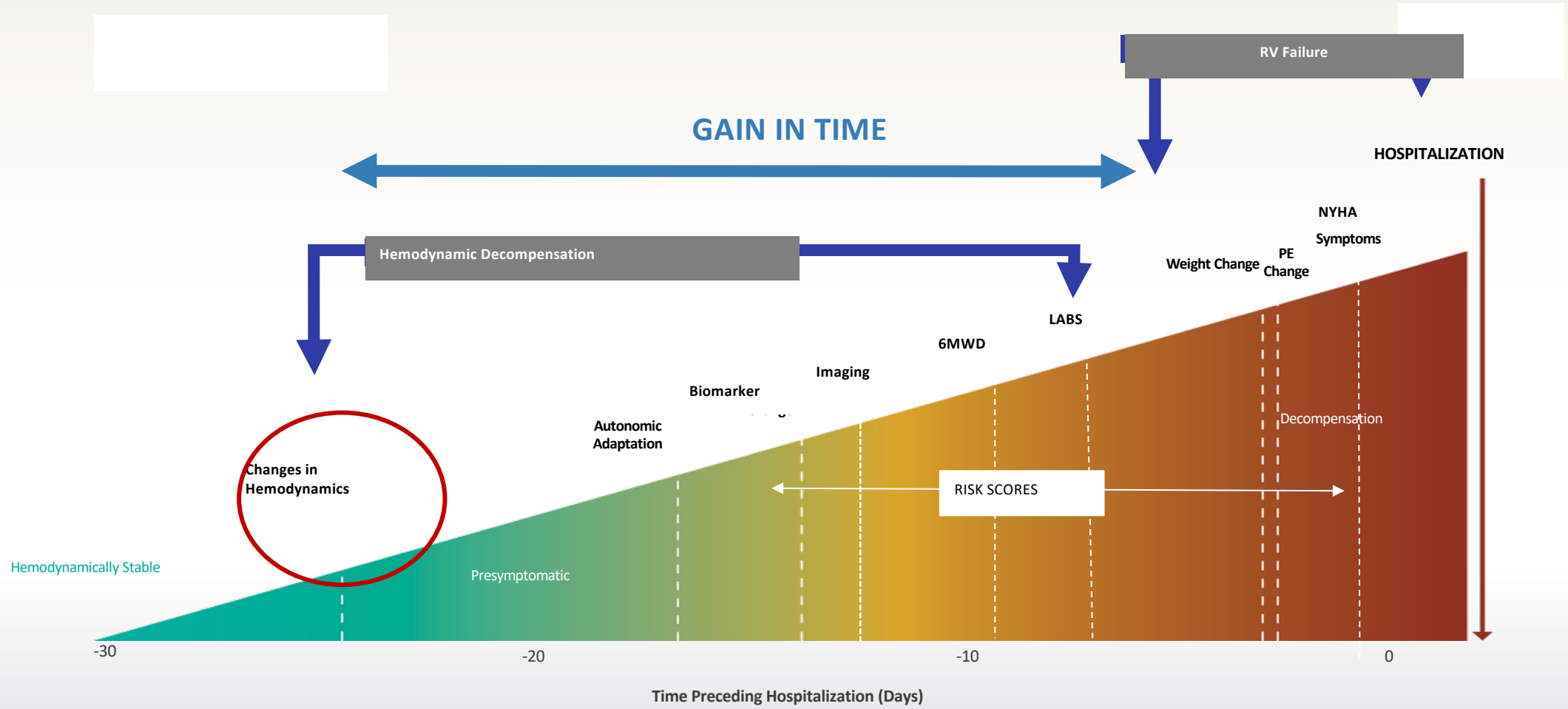
- Right Heart Cath (RHC) to Measure Pulmonary Artery Pressure Remains the Gold Standard for Cardiac Hemodynamics

- Shortcomings of RHC
  - Invasiveness
  - Risk
  - Cost
  - Single time point assessment
  - Supine and rest condition



Right Heart Catheterization

Archetypal Progression of Decompensation in PAH: Early and Remote Detection is Key



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Adapted; Adamson PB, et al. *Curr Heart Fail Reports*, 2009.

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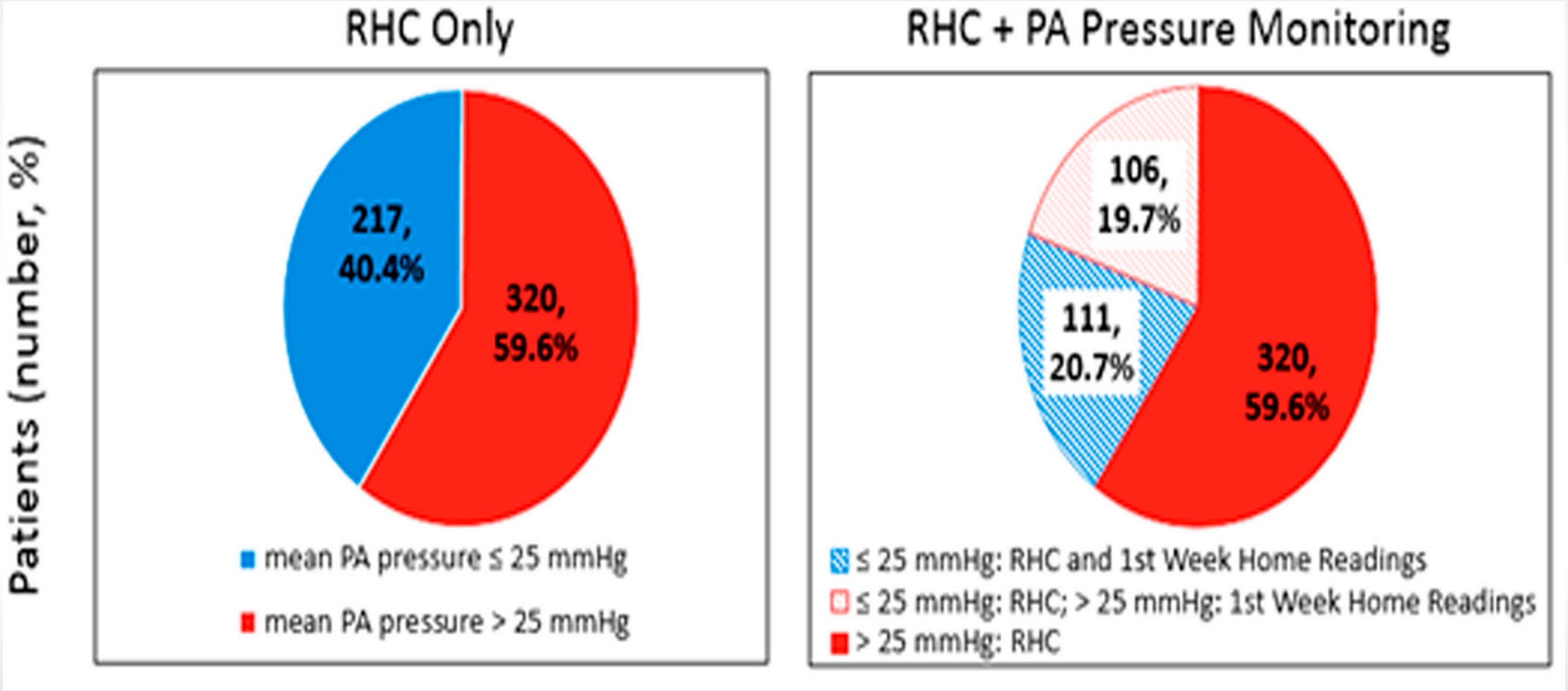
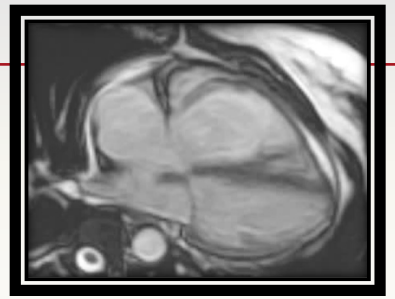
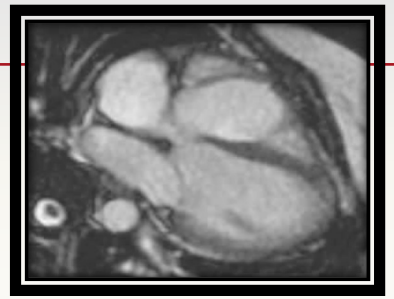
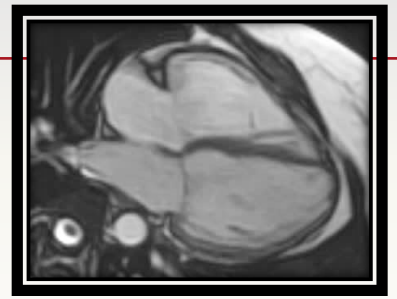
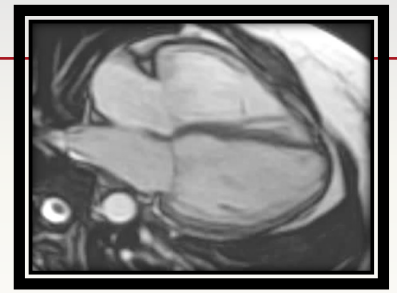
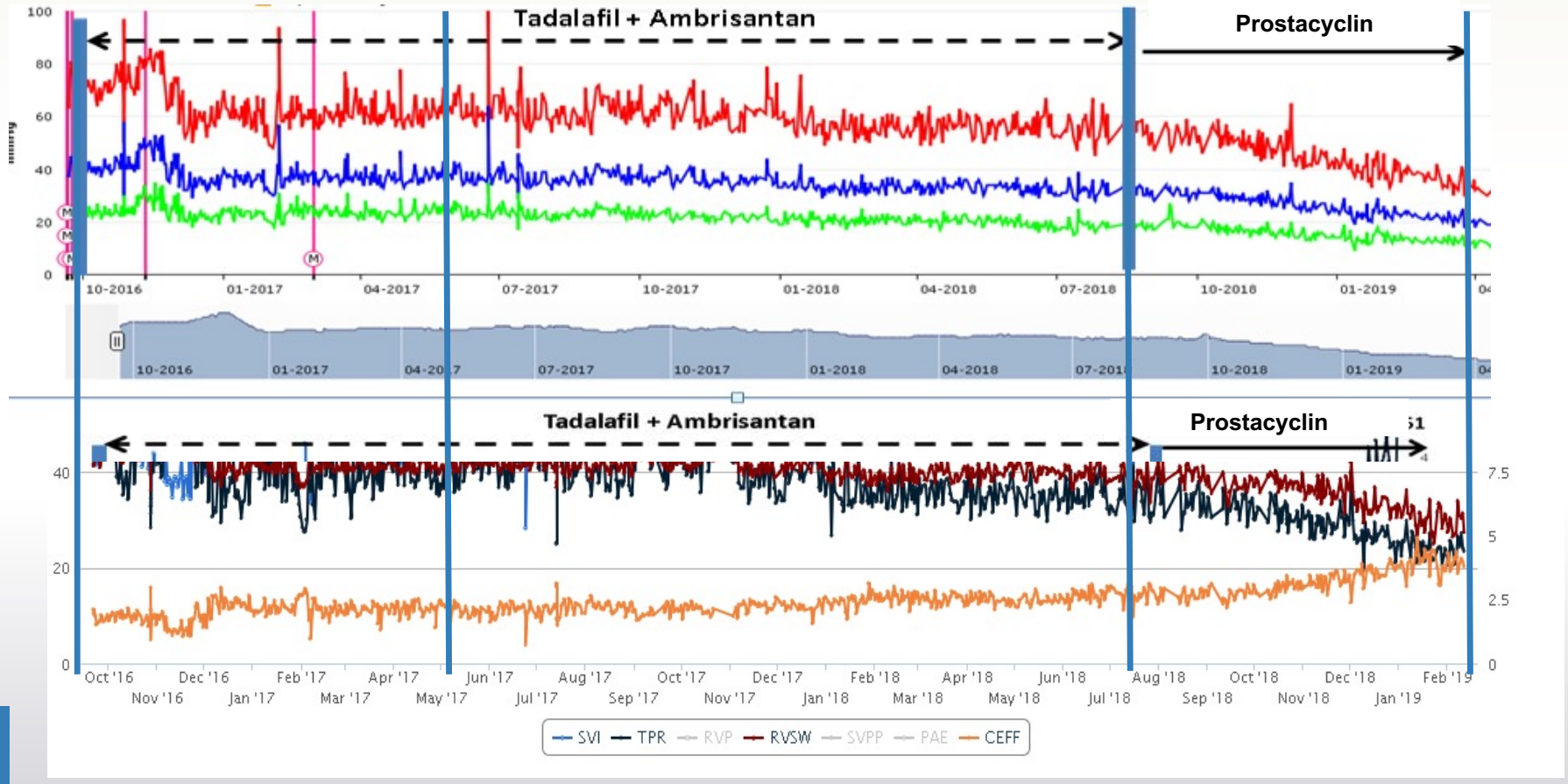
Limitations in Single Point Assessment in Diagnosing Group 2 PHTN by RHC



Changes in Right Ventricular Function with Management of mPAP



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Cereno Scientific

Cereno’s CS1: Phase II study status

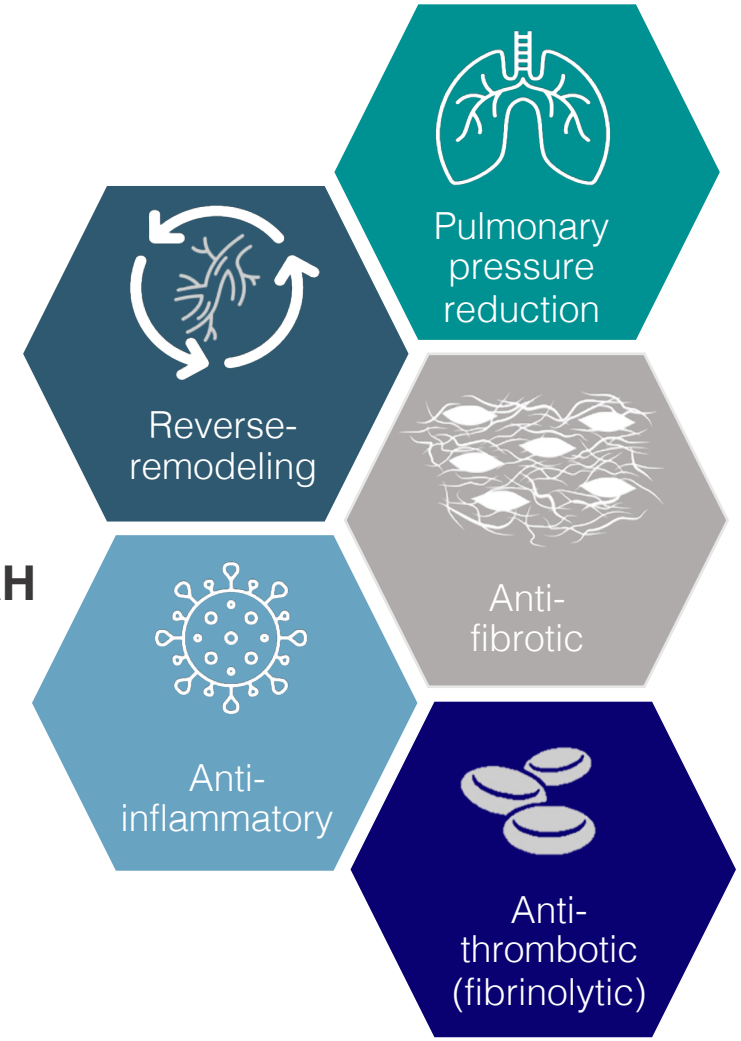
Björn Dahlöf, MD, PhD, FESC, FACC
Chief Medical Officer (CMO), Cereno

Phase II CS1: Focus on developing a disease-modifying treatment for the fatal rare disease PAH

CS1 could fill the significant need for more efficacious and safer therapies with a disease-modifying potential to improve survival and quality of life for PAH patients.*

- CS1 is a new advanced reformulation and acts as an epigenetic modulator through HDAC inhibition
- Proven good safety and tolerability in Phase I study.
- CS1's broad efficacy profile makes it a strong alternative or addition to marketed and pipeline PAH drugs due to **reverse remodeling**.

CS1's multi-fold efficacy, all relevant for PAH pathophysiology



*Currently in Phase II development.

Source: Niklas Bergh (2019) A First-in-Class Treatment for Thrombosis Prevention? A Phase I Study With CS1, a New Controlled Release Formulation of Sodium Valproate. J Cardio Vasc Med 5: 1-12

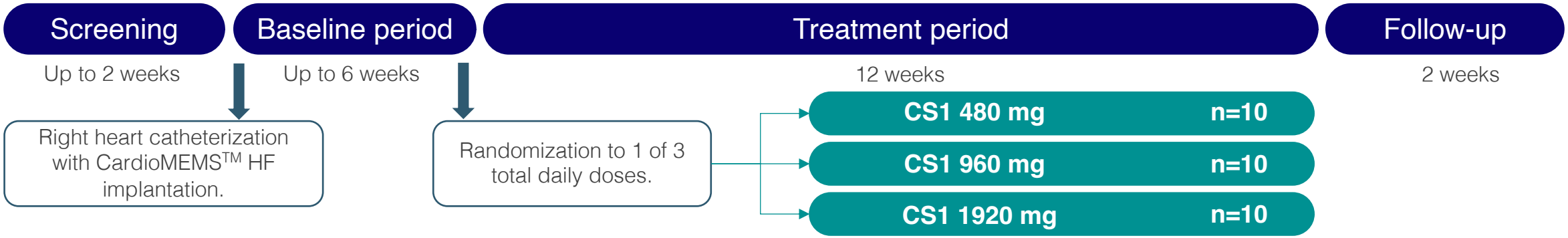
Phase II CS1: Innovative dose-finding study

in collaboration with Abbott

- Primary endpoint: Safety and tolerability.
- Other variables including all standard efficacy endpoints for this patient group (6MWT etc.), a calculated validated risk score, pharmacokinetics, and dose-finding based on mPAP changes.
- Abbott's CardioMEMS™ HF System technology for monitoring pulmonary pressure and pulmonary/RH hemodynamics.
- To include 30 patients, at about 9 (11) different US clinical sites.

Study status

- First site activated: 14 Mar 2022
- First patient screened: 5 July 2022
- First patient randomized: 25 Aug 2022
- All centers activated end Jan 2023
- Activation of new clinical sites is ongoing
- Top-line results are expected Q1 2024



CS1 Phase II: Ongoing study toward key milestones, delayed by a quarter due to slower recruitment in July-August

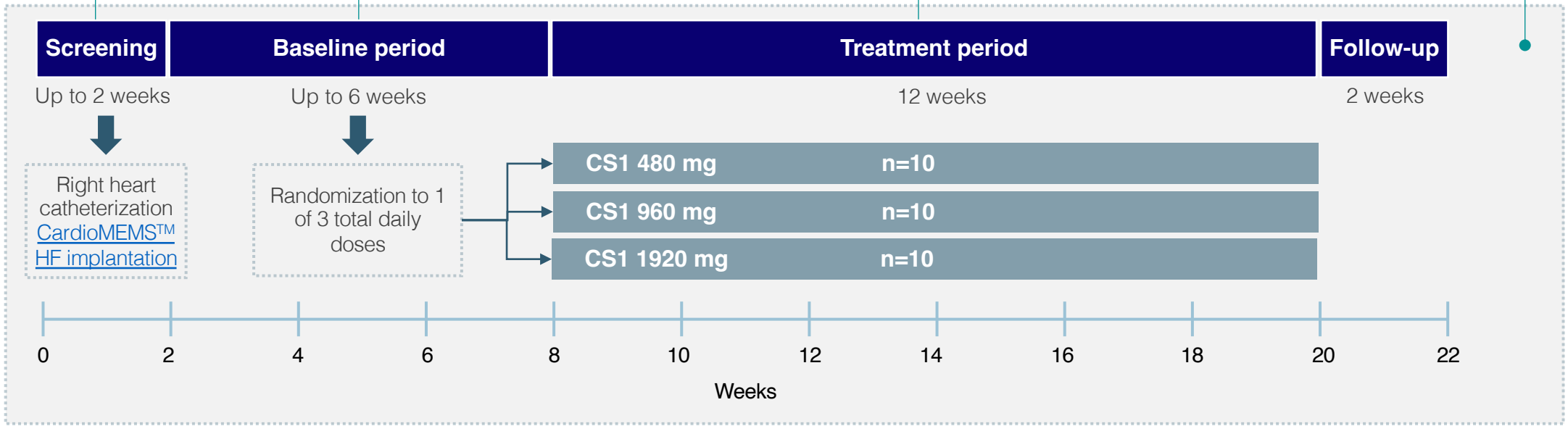
Study status Aug 30

25 patients enrolled

16 patients received CardioMEMS*

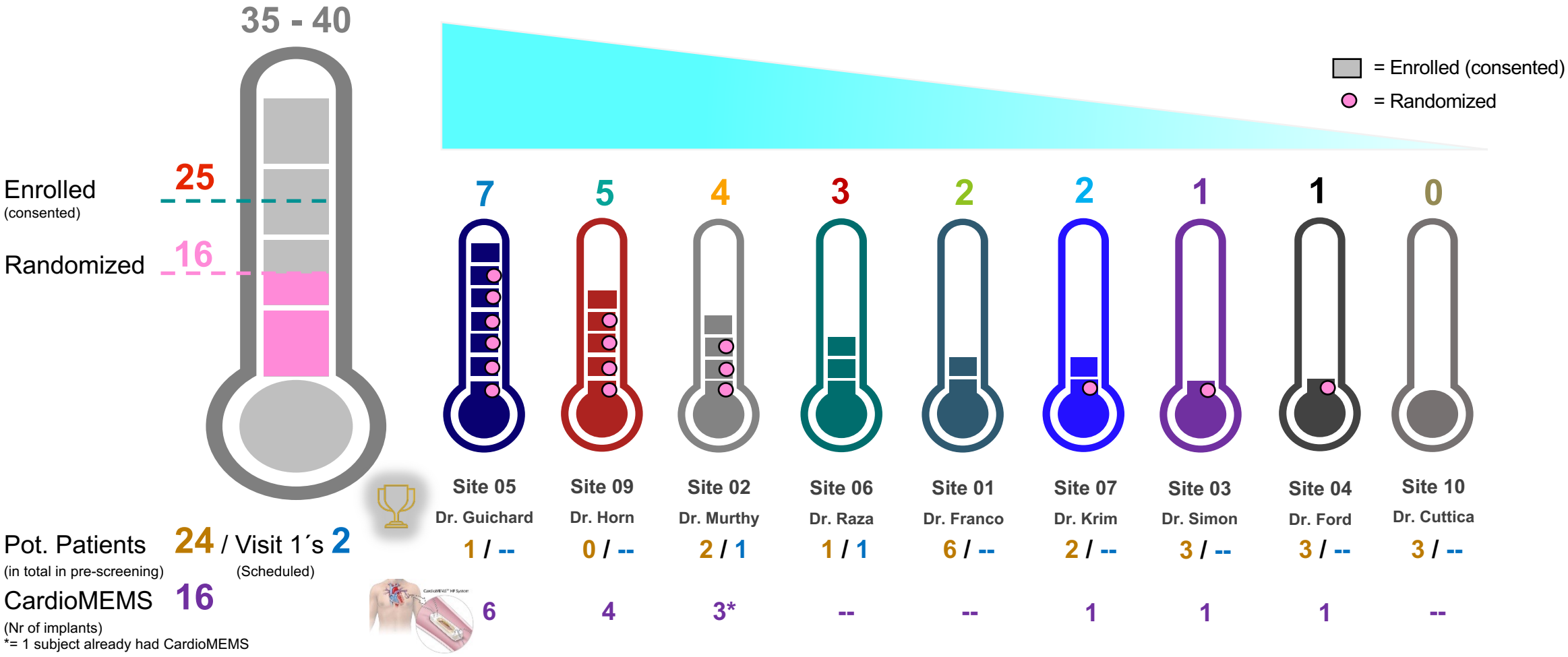
16 patients randomized and in treatment

5 patients completed



Study population: Patients with NYHA/WHO FC II or III PAH class I (male and female, aged 18-80 years, BMI 18-40 kg/m2) with limited exercise capacity, on stable mono or dual combination therapy, and at intermediate/high risk (REVEAL Risk Score 2.0) of clinical worsening. The study is being conducted under the IND accepted by the US FDA September 17, 2021.

Enrolled/Randomized: 25/16



Site Activation Update: All 9 selected sites activated

Two new specialist clinics with large capacities are currently in the start-up phase to be activated to complete the recruitment of patients

Other mitigation strategies

- **Two new sites** with great track record and potential will be activated soon
  - **Potential to recruit approx. 4-5 patients in the study from each new site**.

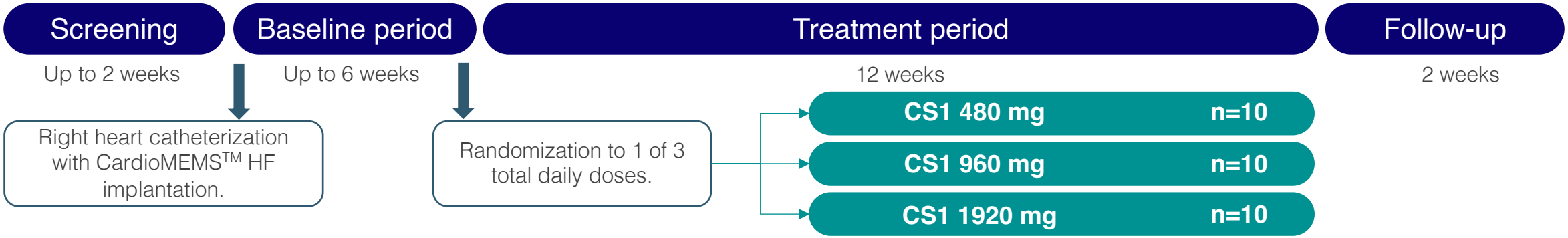
Other ongoing recruitment mitigation strategies

- ✓ Clinical Trial Liaison visits to all sites
- ✓ Dr. Benza to contact all sites to discuss recruitment efforts and expectation to have 2 subjects enrolled in March
- ✓ Clarification regarding stable PAH therapy- completed via Dr. Benza discussions
- ✓ WW to discuss site budgets with SC – specifically subject travel reimbursement
- ✓ Dr. Benza/Site Teleconference re: CardioMEMS HF
- ✓ Weekly Enrollment Blast
- ✓ Weekly monitoring of screened patients by WW, Ray and Cereno team teams conference
  - List of potential topics for publication (rich database)
  - Author Manuscript for 2+ randomized patients

Phase II CS1: Innovative dose-finding study

in collaboration with Abbott

Topline results expected Q1 2024



Cereno Scientific

Cereno's CS1: Remarkable patient case study data

Dr. Raymond L. Benza

System Director of Pulmonary Hypertension at Mount Sinai Icahn School of Medicine, New York City; Chair of Cereno's SAB and PI of Phase II study with CS1

Case Study

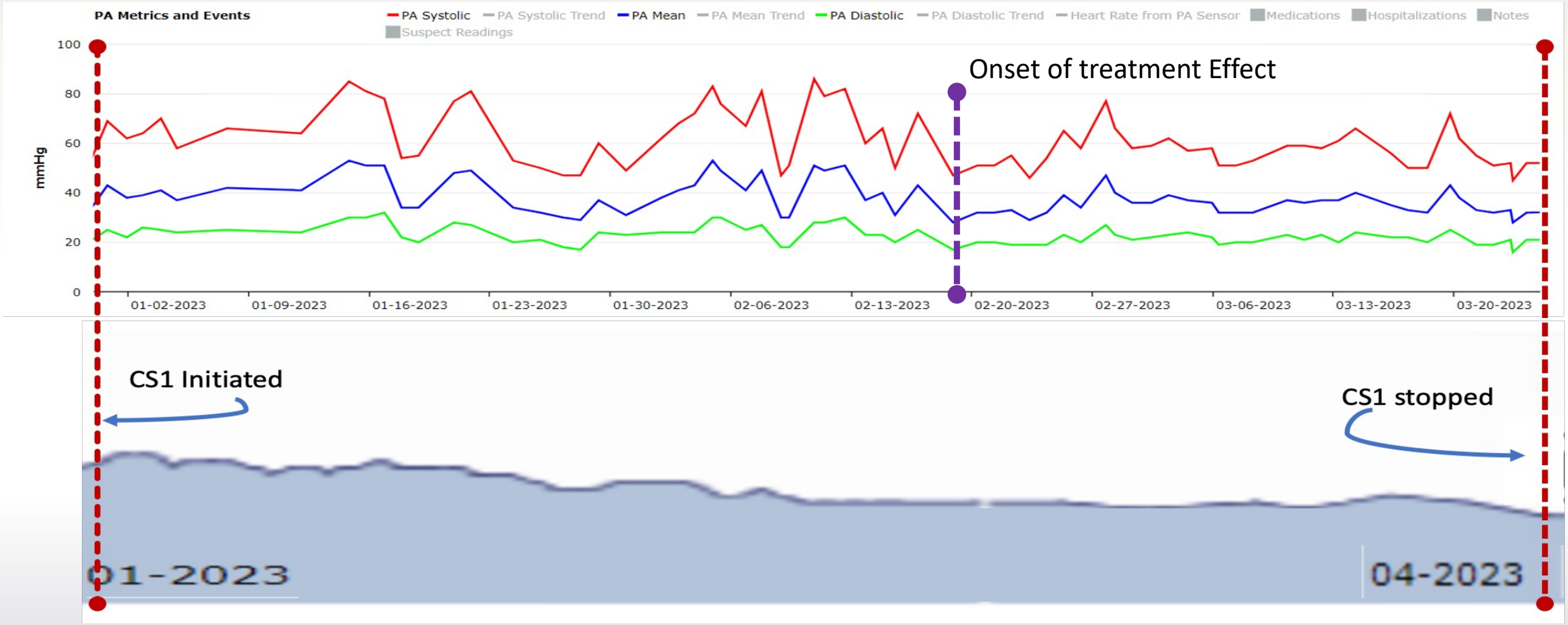
- 51-year-old female patient with symptomatic PAH for 3 years
- NYHA/WHO functional class II
- Six-minute walk distance 446 m.
- Meds: tadalafil 40 mg, macitentan 10 mg, and treprostinil 32 µg dry powder inhaler.
- mPAP 33mmHg CO 4.7 l/min
- The CardioMEMS PA Sensor was implanted in a distal branch of her PA
- Randomized to the 1920 mg dose of CS1

Hemodynamic Changes

Hemodynamic Parameter	Baseline	12 weeks
Mean PAP	33	23
Cardiac Output	4.7	5.6
Total Pulmonary Resistance	7	4

- No changes to her PAH medication during the study,
- Improved to NYHA/WHO functional class I.
- No adverse events related to PA sensor implantation or the device itself.

The CardioMEMS™ HF System Permits Daily Non-Invasive Monitoring of Hemodynamics in A Patient with Pulmonary Artery Hypertension (PAH) Enrolled in A Phase 2 Trial of CS1, A Novel Controlled-Release Formulation of Valproic Acid



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Conclusions

- Using the CardioMEMS PA Sensor permits safe remote monitoring of PA pressure over time in patients with PAH, which permits assessment of medication effectiveness.
- CS1 appeared to lower the mPAP to normal in this patient
- mPAP lowering resulting from improvements in CO and resistance
- Onset of effect possibly as early as 4-6 weeks
- Sets the tone for completion of studies

Cereno Scientific

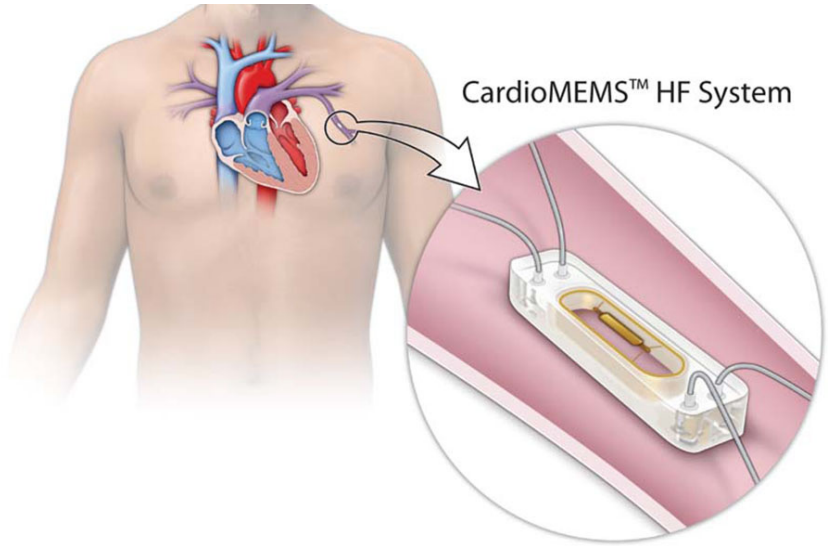
CS1: Launching data quality control initiative in the Phase II study

Björn Dahlöf, MD, PhD, FESC, FACC
Chief Medical Officer (CMO), Cereno

CS1 Phase II PAH Study: Collaboration with Abbott for use of cutting-edge technology CardioMEMS™ provides unique hemodynamic insights on a daily basis

Unique collaboration between Abbott and Cereno with potential to improve the paradigm of medical management of the rare disease PAH.

- CardioMEMS is an implantable pulmonary artery pressure monitoring system device providing daily collection of pulmonary pressure and hemodynamics from the study participants remotely.
- **Benefits for CS1 Phase II study:**
  - **Unique efficacy data points over the full study period.**
  - **Enables a smaller-size population in the Phase II study**
  - **Support definition of optimal dose range for later clinical studies with CS1.**



CardioMEMS HF Monitoring System

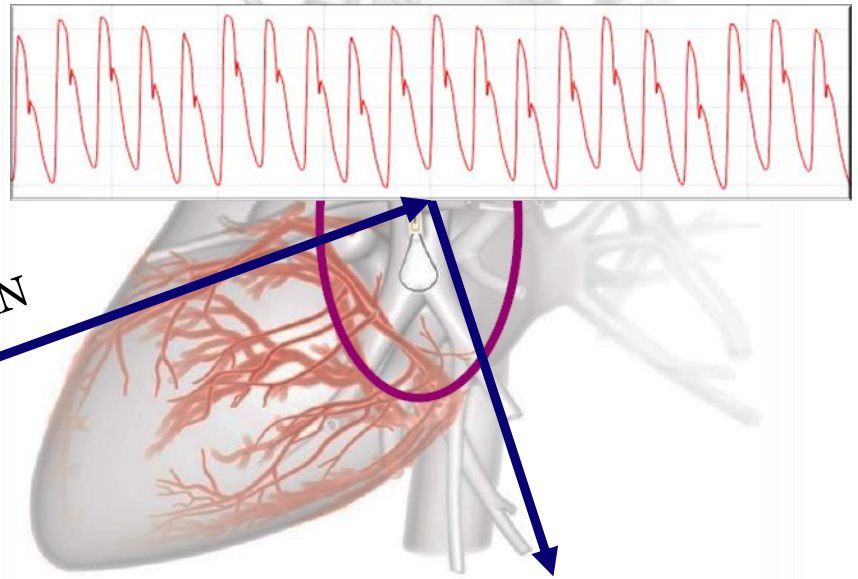
PULMONARY ARTERY PRESSURE SENSOR

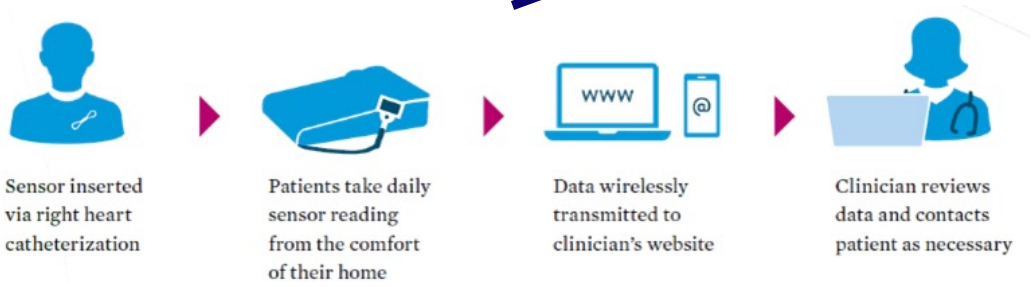
PATIENT ELECTRONICS SYSTEM

MERLIN.NET™ PATIENT CARE NETWORK (PCN)

Upload via cellular or LAN

TARGET LOCATION FOR PA PRESSURE SENSOR





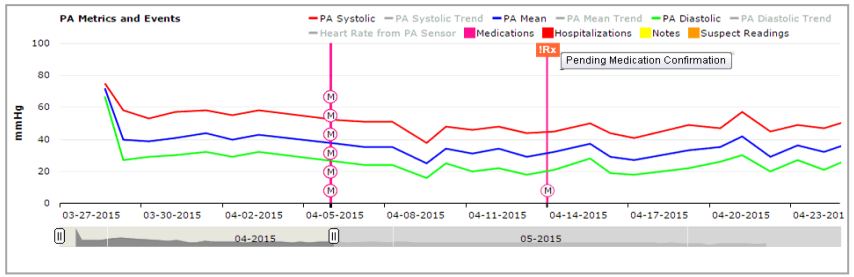
Sensor inserted via right heart catheterization

Patients take daily sensor reading from the comfort of their home

Data wirelessly transmitted to clinician's website

Clinician reviews data and contacts patient as necessary

PA SYSTOLIC, DIASTOLIC AND MEAN. HEART RATE

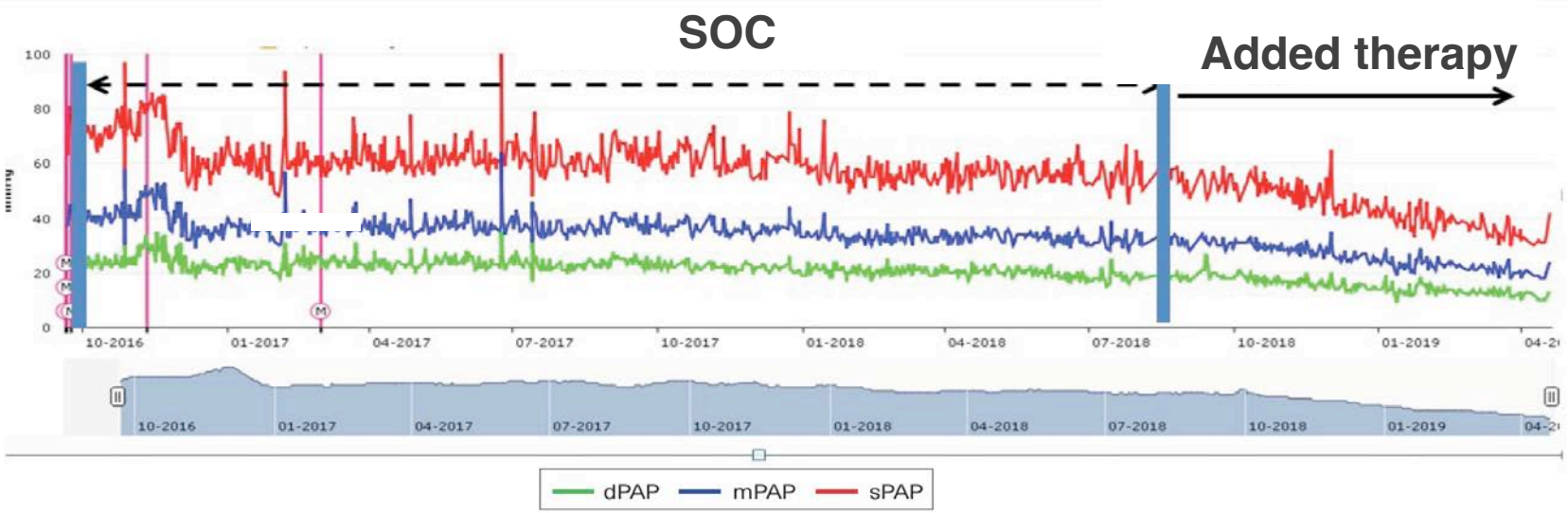


Cereno Scientific

Slide presented courtesy c Abbott

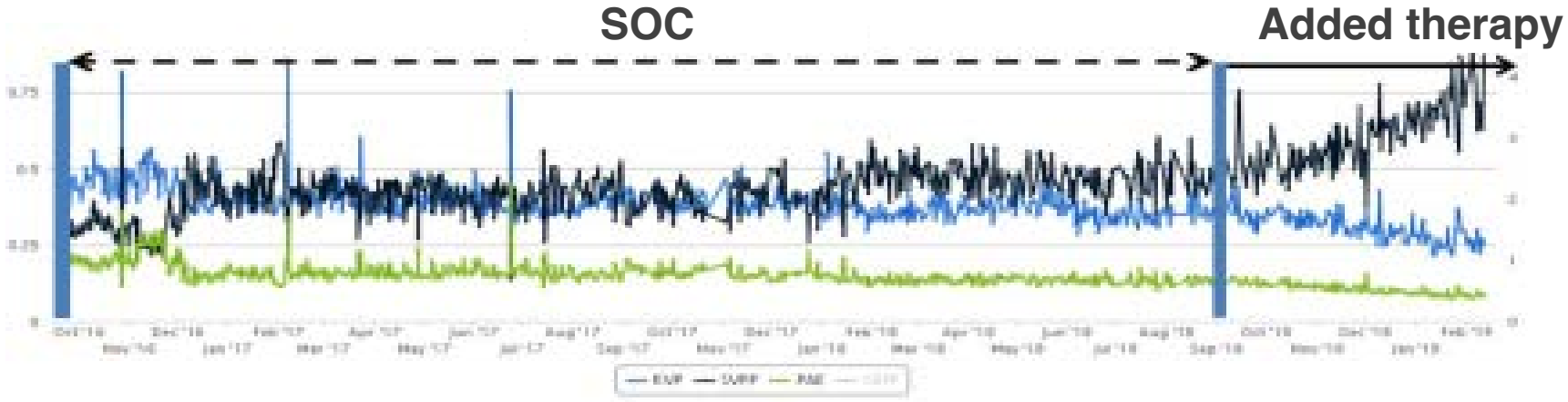
https://clinicaltrials.gov/ (NCT05224531)

Clinical trial design CS1 in PAH-phase II – CardioMEMS an opportunity for evaluating pulmonary hemodynamics and right ventricular function



- Cardiac output and index
- Systolic pulmonary artery pressure (sPAP)
- Diastolic pulmonary artery pressure (dPAP)
- RV stroke work and stroke work index
- RV efficiency (SV/mPAP)

- Total pulmonary resistance
- SV, SVI
- Pulmonary compliance
- Pulmonary elastance
- Cardiac efficiency
- Cardiac power

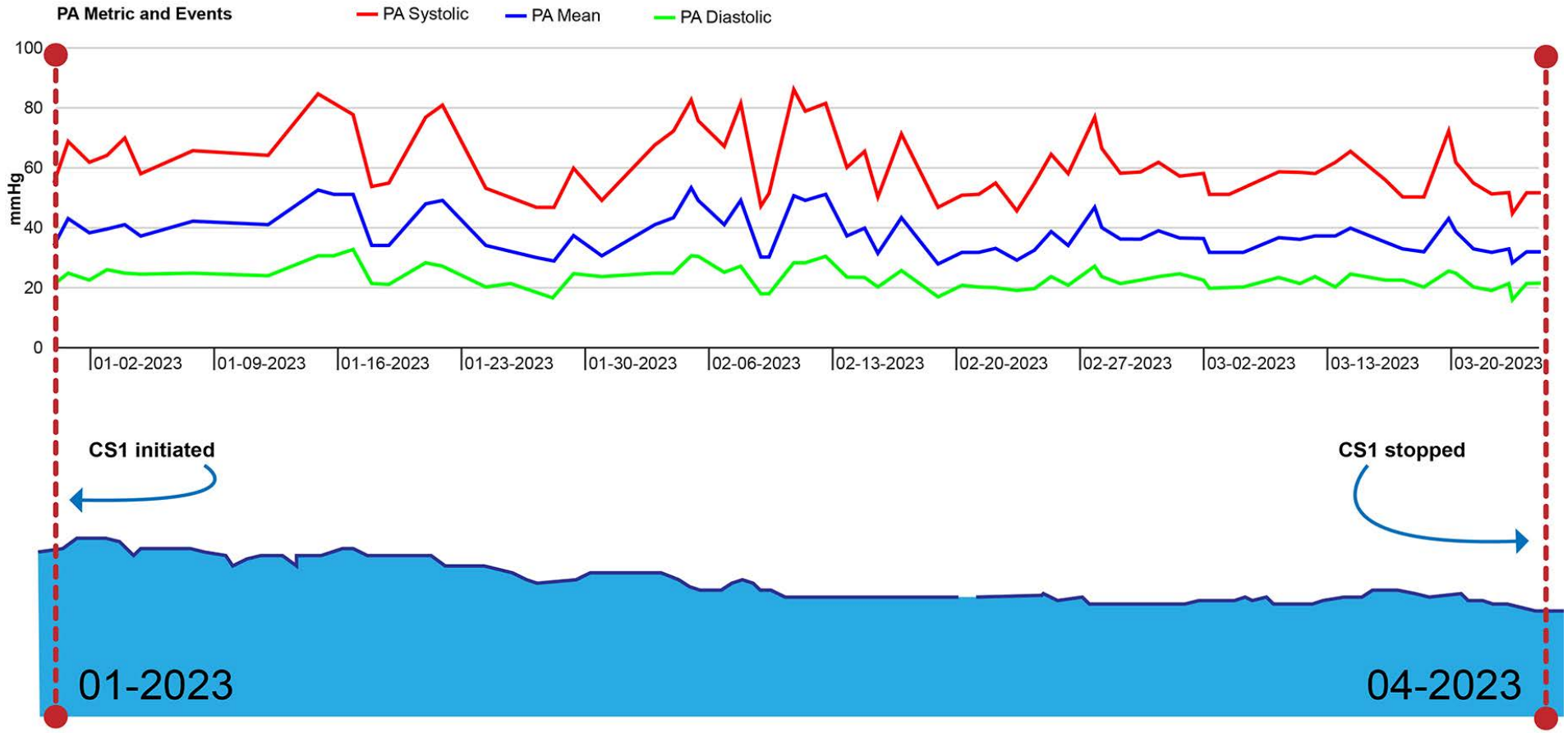


Cereno Scientific

Abbott

Courtesy Dr Benza

Pulmonary artery pressure changes over time as shown in a 51-year-old female patient with PAH on stable SOC therapy in CS1 Phase II study using the CardioMEMS PA sensor



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https://clinicaltrials.ov/ (NCT05224531)

Sample Size

From the protocol

10.2 Sample Size

The primary objective of the study is to obtain safety and tolerability data.

Sample size is calculated based on estimates of effect on mPAP. The mPAP analysis is based on multiple readings which will increase the precision of pressure determination. A sample size of 10 in each group will have 80% power to detect a difference in means of 15%, assuming that the common standard deviation is 5 with a 5% significance level.

Due to the unique power of CardioMEMS to evaluate pulmonary hemodynamics, it is possible to see a clinically relevant effect on pulmonary pressure on an individual level as illustrated by the patient's case

CS1 Study – Primary and secondary endpoints

Primary endpoint

Safety and tolerability as measured by:

- AEs
- Adverse events of special interest (AESIs)
- Serious adverse events (SAEs)
- Adverse device effects (ADEs) related to the CardioMEMS™ HF system incl. unexpected serious adverse device effects (USADEs)
- Laboratory parameter abnormalities
- Change in vital signs
- Bleedings
- Change in ECG parameters

Secondary exploratory endpoints

Change from baseline and difference between doses

- **Pulmonary Vascular Resistance, cardiac /pulmonary hemodynamics from RHC**
- **RRS 2,0**
- **REVEAL lite 2**
- **Pharmacokinetics**

- Need for additional therapy
- NYHA/WHO FC
- Quality of life (SYMPACT)
- Minnesota Living with HF Q
- Hospitalizations; PAH related and other
- CV morbidity and mortality; PAH related/other

- **6MWD**
- **Actigraphy**

- eGFR
- NT-pro-BNP, ST2, PAI-1
- Other biomarkers TBD (Biobank)

- **From CardioMEMS™**
  - sPAP, dPAP, mPAP
  - Other calculated RV variables and TPR
- **Echocardiography**
  - Morphology and Function Left Ventricle
  - Morphology and Function Right Ventricle
- **MRI in sync with CardioMEMS™**
  - Morphology and Function Left Ventricle
  - Morphology and Function Right Ventricle

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https://clinicaltrials.gov/ (NCT05224531)

Monitoring of the quality of data collected from CardioMEMS

Rationale:

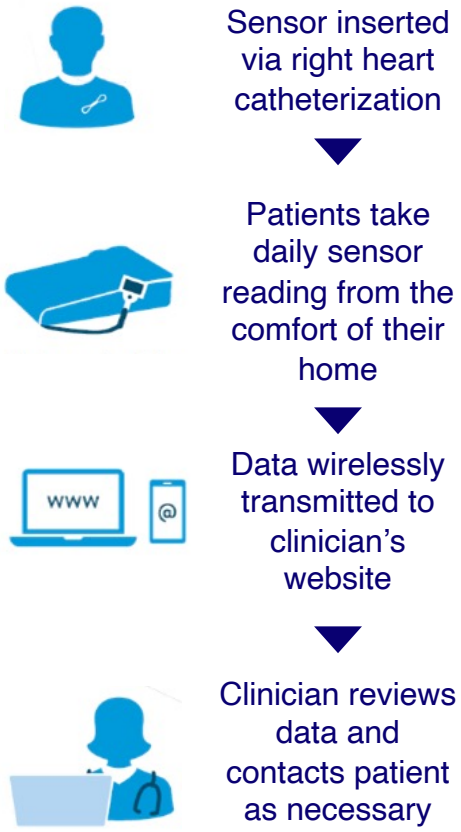
- **Use of "new innovative technology in a new patient category".**

Scope:

- Collect and review the data from the CardioMEMS device, captured in a central database. **Review blinded pressure data for all randomized patients from baseline to end of study**, or to the latest data sampling point if the patient is still on study medication during the study.

Outcomes:

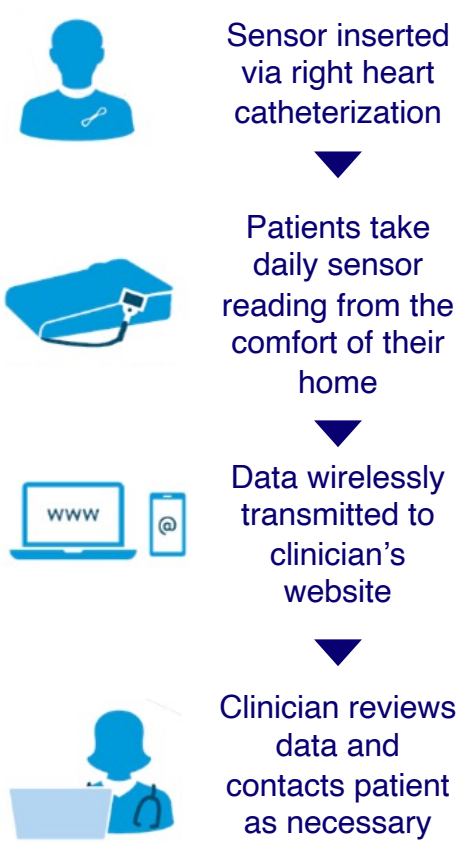
- **Pulmonary arterial pressure measurements for all randomized patients from baseline and weekly up to last measure**



Monitoring of the quality of data collected from CardioMEMS

Implications:

- A potential overall treatment effect of intervention may be observed at an earlier stage.
- A potential positive communication: **High quality data by use of novel technology in a new patient population and preliminary general statement on CS1 efficacy in pressure reduction**, however, without guidance on dose response.



Cereno's initiative for data quality control of CardioMEMS will provide an opportunity to have an early efficacy read-out in Q4

June 2023

The **remarkable patient case** triggered the initiative for data quality control of CardioMEMS measurements **to ensure optimal data quality**.

August 2023

Cereno announced an **initiative to control the data quality** produced from the cutting-edge technology **CardioMEMS** used to monitor pulmonary pressure and other cardio-pulmonary hemodynamics during the Phase II study.

Q4 2023

Opportunity for early signs of CS1 efficacy on pulmonary hemodynamics e.g mPAP

Q1 2024

Ultimately, the data quality control will **support a conclusive study results from this new CardioMEMS HF System technology in a new disease indication**.

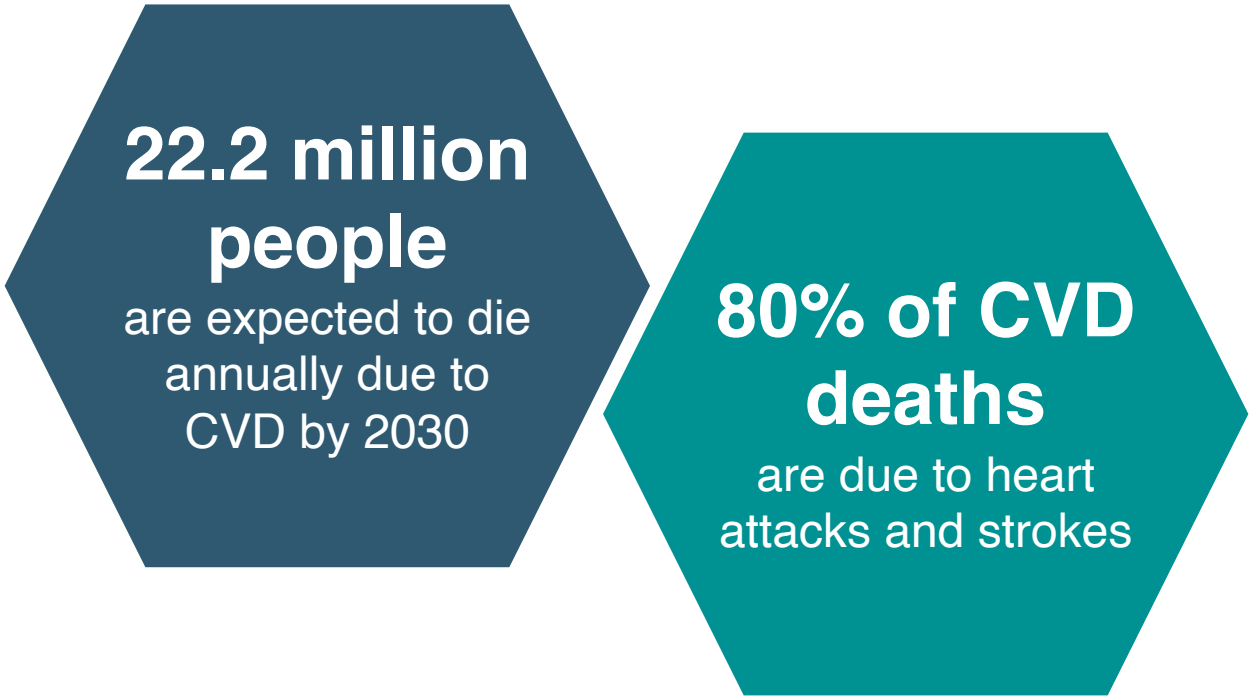
Cereno Scientific

Medical need in cardiovascular disease – new strategies to meet growing prevalence

Björn Dahlöf, MD, PhD, FESC, FACC
Chief Medical Officer (CMO), Cereno

More than 200 million people in the world today are at high risk of having a cardiovascular event

Cardiovascular disease (CVD) is a group of disorders of the heart and blood vessels.



WHY?

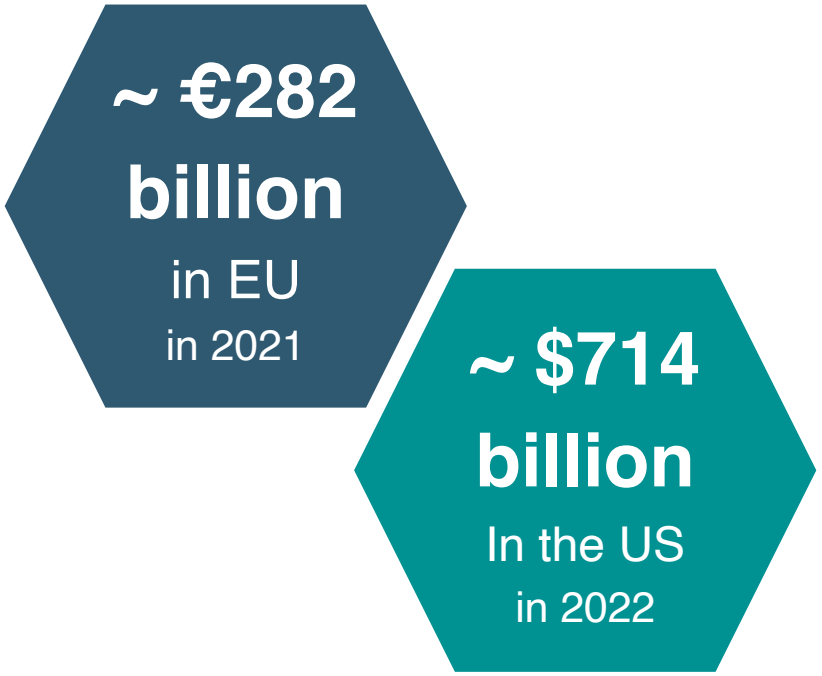
Most CVD complications happen because of thrombus formation – blood clots obstructing the cardiovascular system.

Existing treatment options are insufficient.

Cardiovascular disease equals exorbitant costs for patients, their families and society

- Cereno has focused on two areas: **thrombosis** and **PAH**
- **Common and rare CVDs result in significant markets** due to their morbidity, adverse effect on quality of life and threat of mortality
- The **global anti-thrombotic drug market** is estimated to grow on average **7.5%** per year, resulting in a **$43.4 billion** market by **2025.**
- **$USD 11.7 billion** is the estimated global market size in 2027 for rare disease PAH – a Cereno target indication
  - **6.2%** is the estimated market increase for 2021–2027.
  - Growth is expected to be driven by increasing prevalence rates as well as government support for development of orphan drugs.

Societal annual cost of CVD



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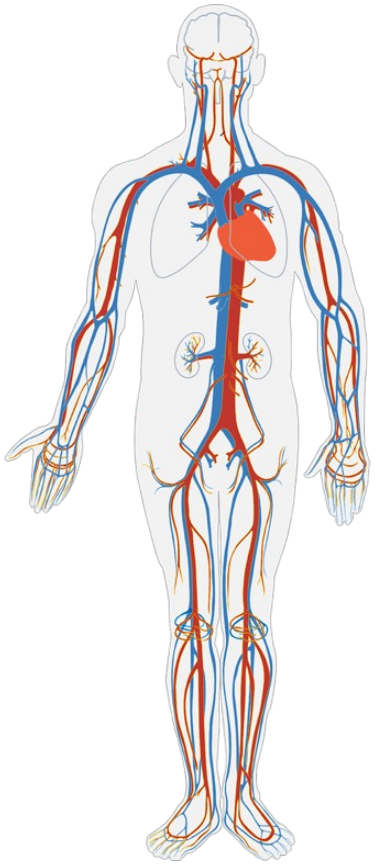
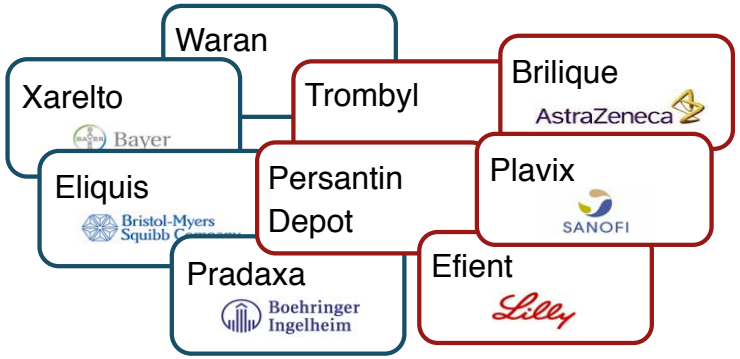
Sources: Luengo-Fernandes et al., 2023 (link), American Heart Association (link) – 2017 data, Epigenetic Modulation for Cardiovascular Disease. Infogence Global Research (2021) "Global Pulmonary Arterial Hypertension (2021-2027)", MSC Nordics analysis.

Major challenge in cardiovascular disease treatment is the side effect of serious risk of bleeding



Current anti-thrombosis/blood thinning treatments involve the risk of serious bleedings

- Common treatment targets systemic inhibition of coagulation/platelet function



Increased risk of bleeding gives insufficient preventive effect, due to under treatment and under dosing

Need for new preventive strategies, with improved efficacy and less or no risk of bleeding

The high bleeding risk with VKA and DOACs impacts patients lives significantly

- **Bleeding is a major adverse event of current anti-thrombotic treatments,** with an annual risk of **major bleeding** of about **2% to 4%[1].**
- Fear of major bleeding complications such as **intracranial hemorrhage (ICH) or massive gastrointestinal bleeding with a high risk of mortality** deters many patients and physicians from initiating treatment with anticoagulants[4].
- **Clinically relevant non-major bleeds** generate a perception of reduced quality of life and thereby decrease the compliance of the patient on anticoagulant treatment[4].

Most common types of major bleeds in trials comparing VKAs with DOACs

Indication	No. of trials	Type of major bleed	VKA	DOAC
Atrial fibrillation	4	All major bleeds	1769	2091
		Gastrointestinal	583 (33%)	1005 (48%)
		Intracranial	425 (24%)	272 (13%)
VTE treatment	7	All major bleeds	263	161
		Gastrointestinal	83 (32%)	50 (31%)
		Intracranial	45 (17%)	17 (11%)

Note: Above table depicts the results from two different systematic meta analyses of > 30 randomized control trials combined and evaluating > 200,000 patients[1-5]

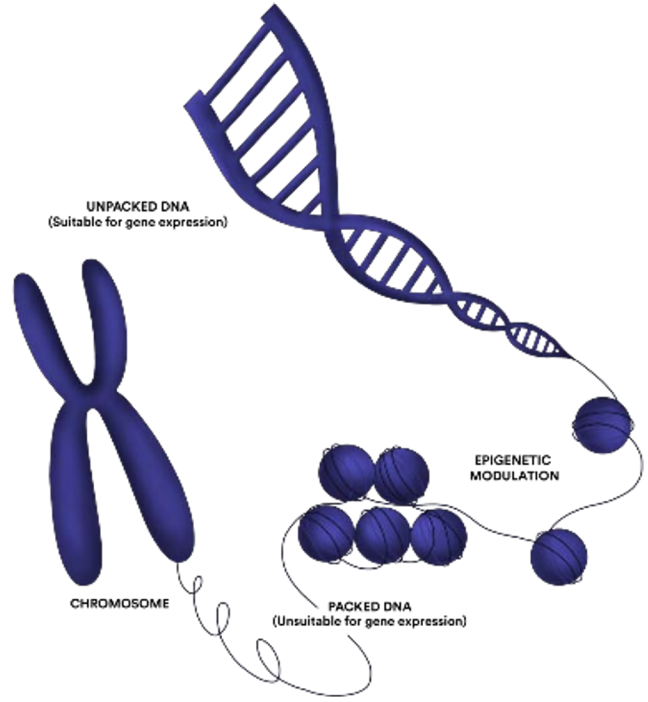
Source: 1. Hematology Am Soc Hematol Educ Program. 2019; 2. Souverein et.al. 2020 (Link), 3. Cipkar C. et.al 2019 (Link), 4. S. Piran & S. Schuman, 2019 (Link), 5. Freehan M. et.al. 2017 (Link)

Epigenetic modulation mediated by HDACs has been identified as an important factor contributing to **CVD and PAH** pathophysiology

The **multifactorial nature of PAH** indicates that **epigenetic factors can bridge genetic and environmental risk** factors for the disease where **mortality remains high**.

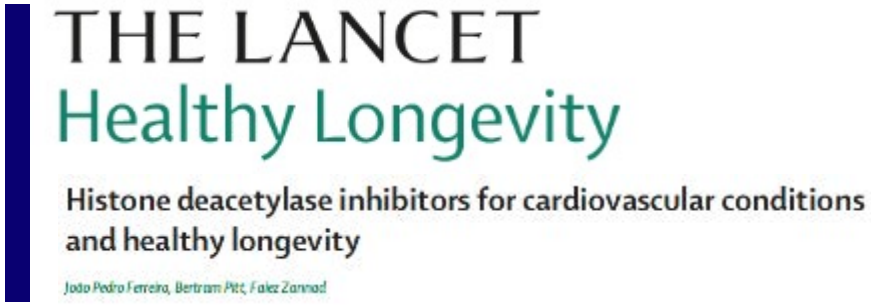
- Epigenetic mechanisms refer to heritable traits that modify gene expression without changing DNA sequence. One of the epigenetic mechanisms through which gene expression can be modulated includes histone deacetylases (**HDACs**).

- **HDAC inhibitors have demonstrated promising results** in cancer, which has further promoted R&D to explore the full potential of HDAC inhibitors **in cardiovascular diseases** in general and **PAH** specifically.



Review article in *The Lancet Healthy Longevity* supports the potential of epigenetic modulation via HDACi in CVD

Accumulating evidence supports the role of epigenetic modulation through HDAC inhibition in the treatment of multiple medical conditions beyond the treatment of epilepsy, which has been documented as the first indication to be treated with the HDACi valproic acid (VPA).



"Given the pleotropic properties of CS1's active substance being a HDACi with documented anti-thrombotic, anti-inflammatory, anti-fibrotic and pressure-reducing effects gives it a unique position to be developed for a variety of cardiovascular diseases with a disease-modifying potential."

– Review article co-author and member of Cereno's SAB, Prof Faiez Zannad, MD.*

Strong potential in cardiovascular treatment and prevention

Myocardial infarction
Heart failure
Pulmonary arterial hypertension
Stroke
Peripheral artery disease
Atrial fibrillation
Arterial hypertension

Cereno Scientific

Source: Ferreira JP, Pitt B, and Zannad F, Lancet Healthy Longev 2021;2,e371-379 doi
*BioStock. Cereno Scientific drives a paradigm shift in CVD. June 11, 2021

Cereno's portfolio has potential to improve the management of CVD compared with today's alternatives in thrombosis

	Common use today			
	Warfarin	NOACs/ Antiplatelets	CS585	CS1, CS014
Dose monitoring not required	Required	✓	✓	✓
Anti-thrombotic efficacy	✓	✓	✓	✓
Lower risk of bleeding	Increased bleeding	Increased bleeding	✓	✓
Organ protection	Not documented	Not documented	Not documented	✓¤

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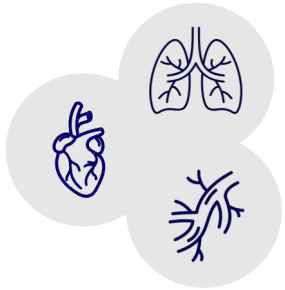
¤ and anti-fibrotic,reverse remodeling, anti-inflammatory, CV protective e,g, in MI and stroke, neuroprotective, reduction pulmonary pressure shown for VPA

Promising programs with potential to transform the CVD treatment landscape



Program	Indication	Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Upcoming milestone
CS1	PAH	HDACi with epigenetic effects					Phase 2 top-line data: Q1 2024
CS014	Thrombosis	HDACi with epigenetic effects					Phase 1 IND submission: H1 2024
CS585	CVD	Prostacyclin receptor agonist					Ongoing Preclinical development 2023/2024

PAH = Pulmonary Arterial Hypertension; CVD = Cardiovascular Diseases, VPA = Valproic Acid, NCE = New Chemical Entity, HDACi = Histone Deactylase Inhibitor

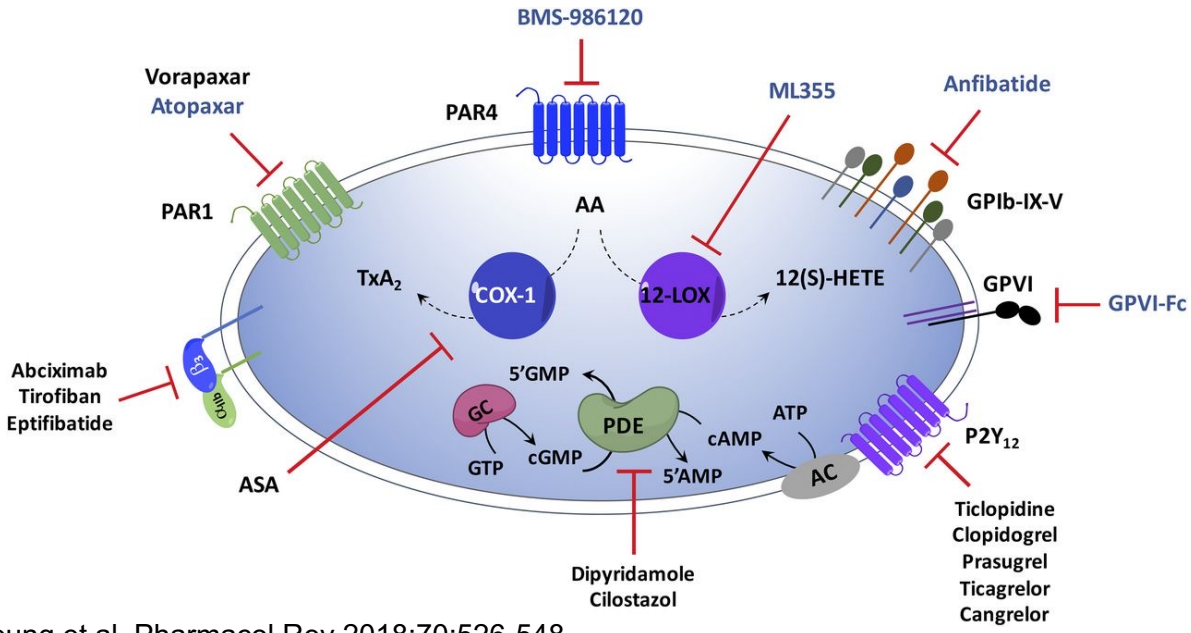
Cereno Scientific

Preclinical programs with potential in thrombosis without increased risk of bleeding

Dr. Michael Holinstat
Prof. at University of Michigan Medical School; and Director Translation Research, Cereno

Thrombosis is a leading cause of morbidity and mortality

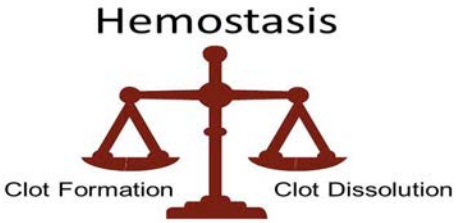
- Anti-platelet drug therapy has reduced the risk of morbidity and mortality due to cardiovascular disease by 25%.
- However, morbidity and death resulting from cardiovascular events triggered by thrombosis remain a significant problem.



New therapeutic approaches are warranted to:

1. Decrease platelet activation and clot formation.

2. Limit the risk of bleeding.



Yeung et al. Pharmacol Rev 2018;70:526-548.

CS014 and CS585 Thrombosis programs

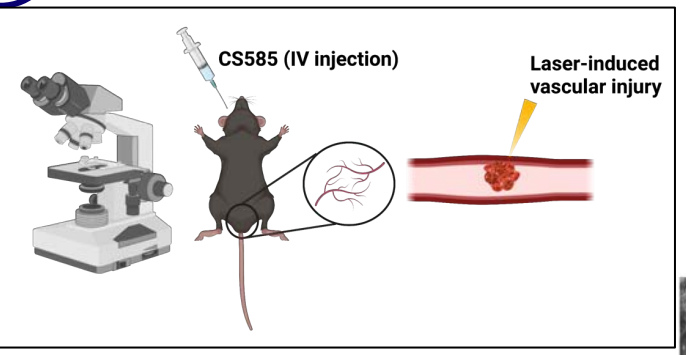
CS014

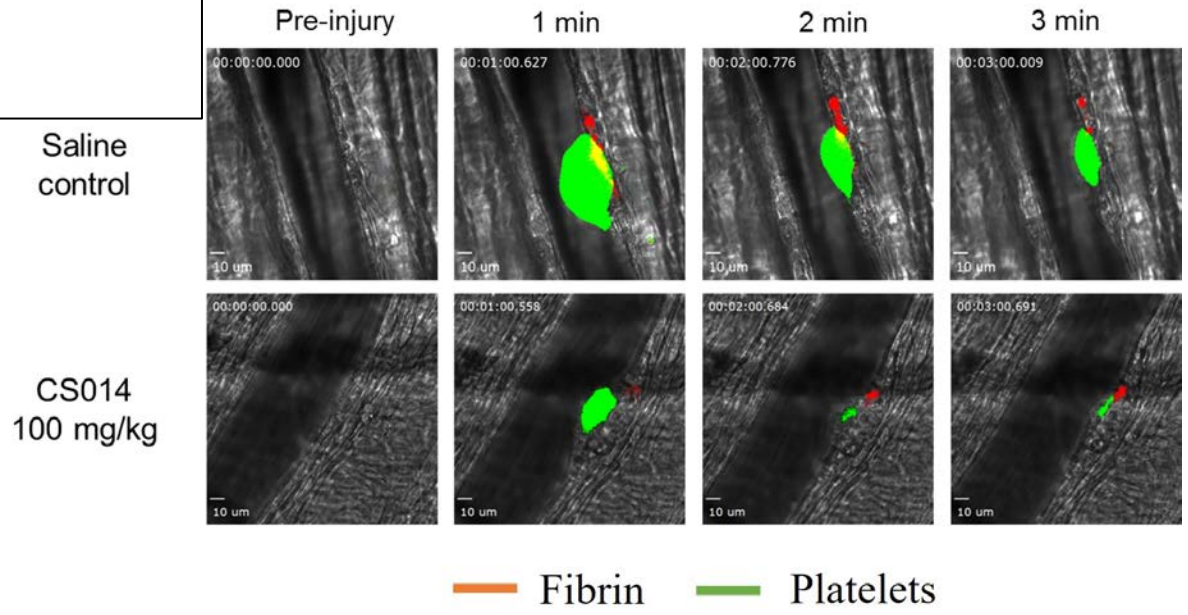
- HDAC inhibitor
- For use in decreasing platelet accumulation and fibrin formation in the vessel
- May additionally function to limit thrombosis without increased bleeding

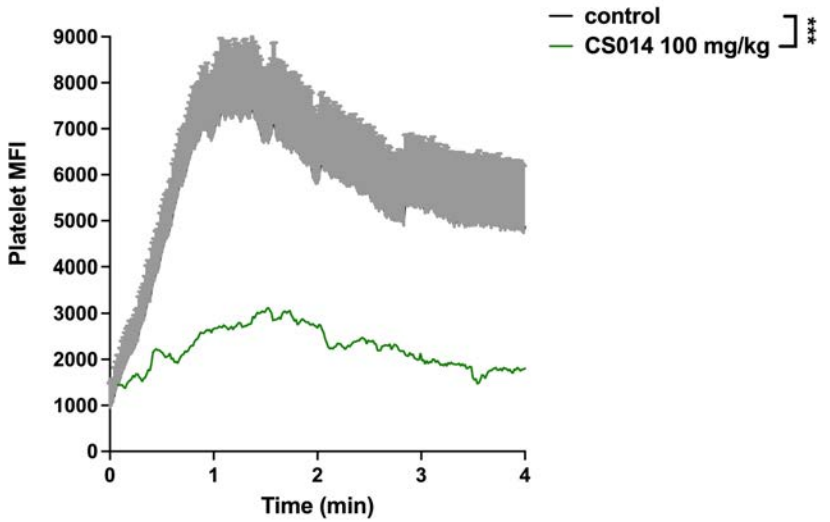
CS585

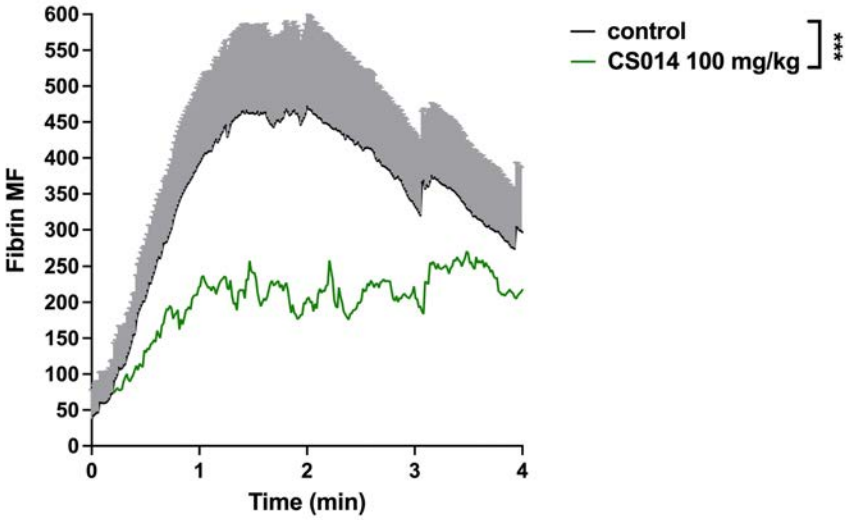
- IP receptor agonist
- Inhibits platelet function and thrombosis through formation of cAMP in the cell
- Hits the same target (IP receptor) as:
  - Iloprost
  - Selexipag/Ralinepeg
- Prevents platelet activation and thrombosis without increased bleeding
  - ➢ Stanger et al. *Blood*, 2023, In Press

CS014 developed as an HDAC inhibitor with the ability to inhibit platelet clot formation following vascular injury





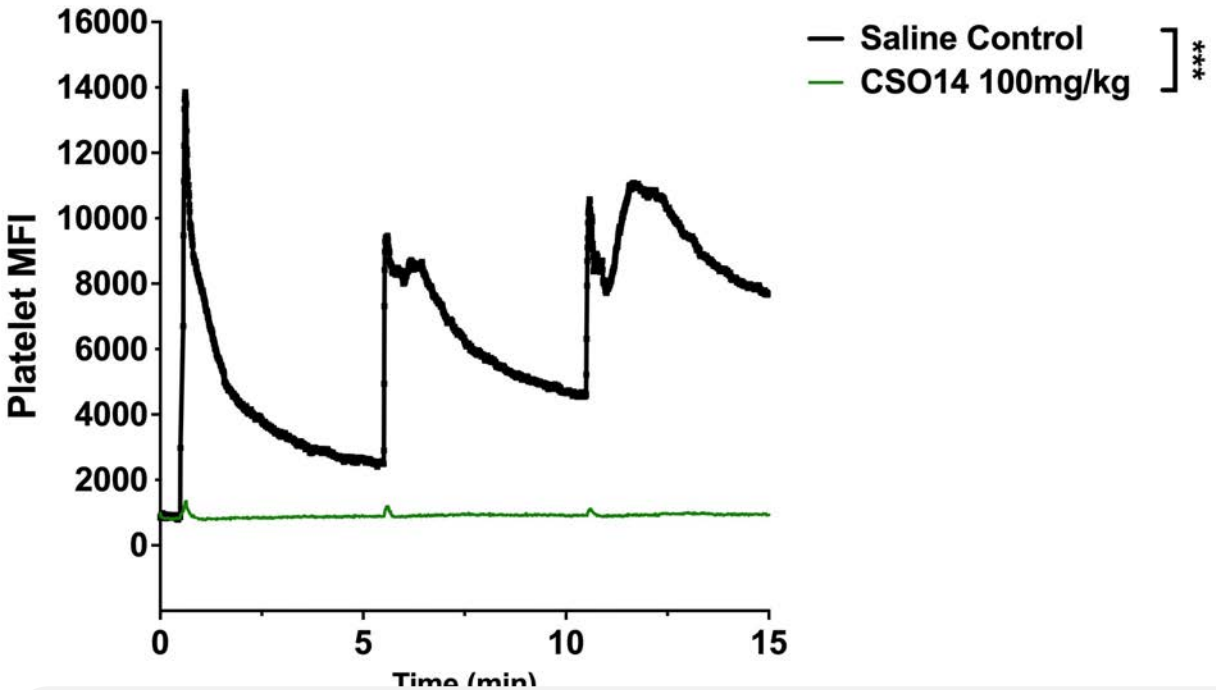


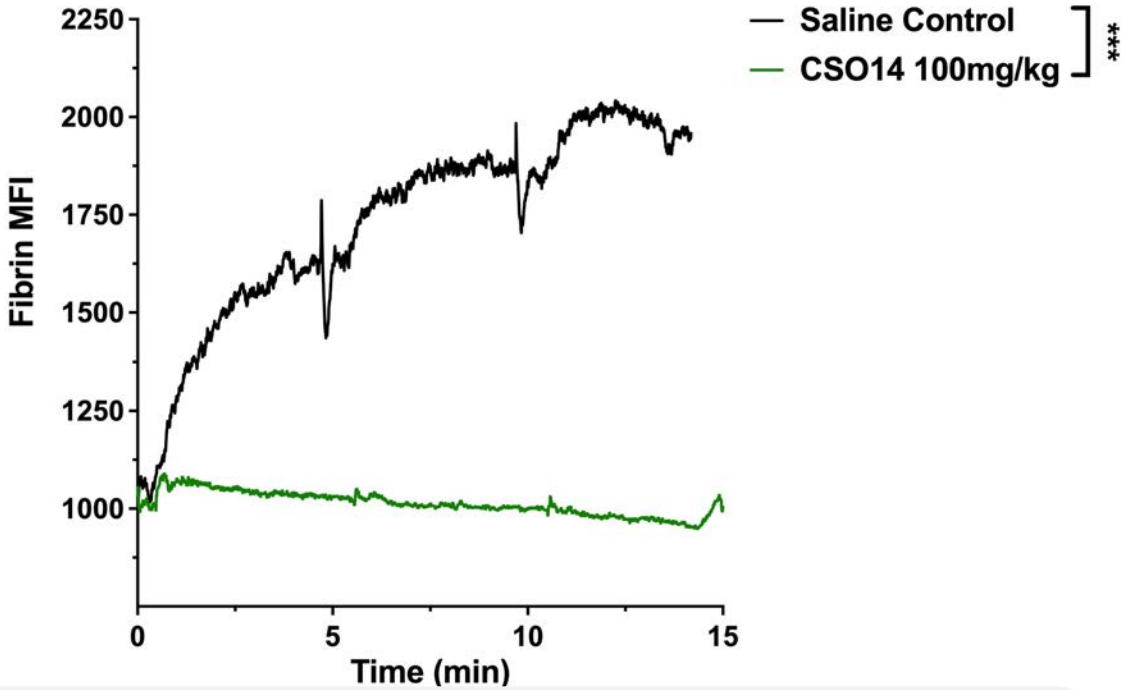


CS014 inhibits thrombosis by:

- **Attenuating platelet activation and clot formation at site of injury**
- **Significantly reducing fibrin formed a the site of injury**

CS014 prevents low shear clot formation and fibrin formation

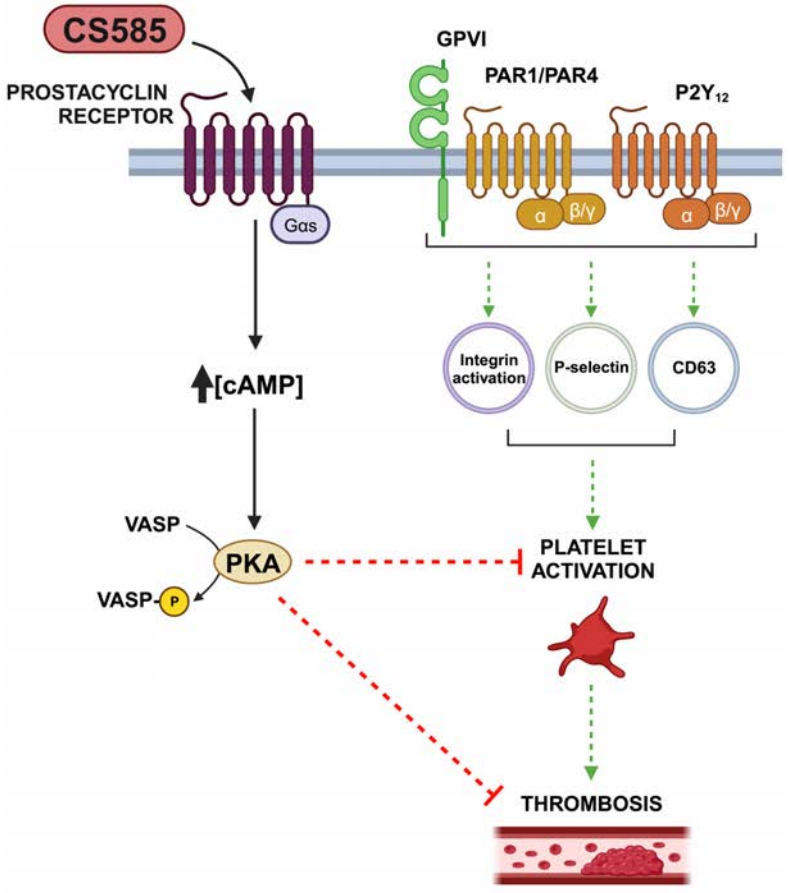


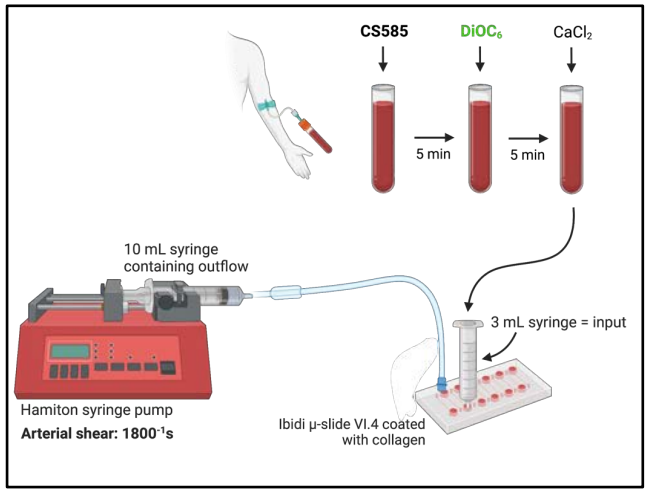


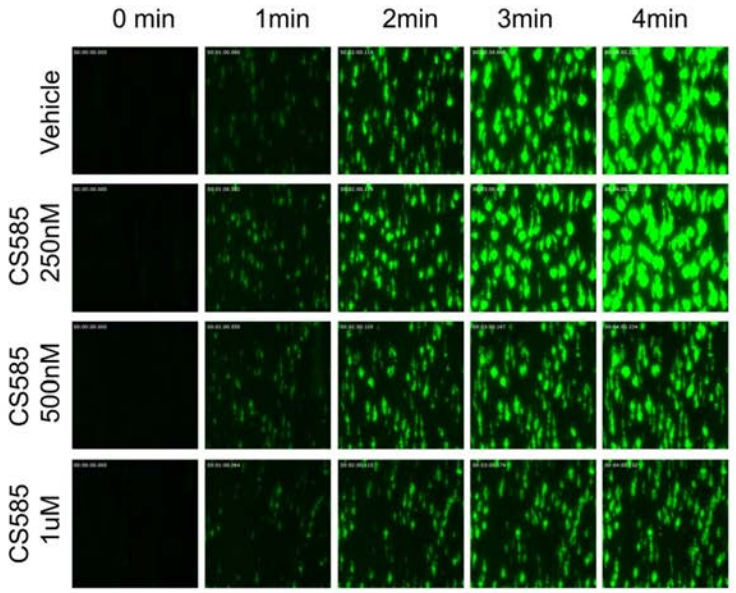
- CS014 prevents platelet clot formation following repeated vessel puncture in the saphenous vein (green).
- CS014 prevents fibrin formation following repeated vessel puncture in the saphenous vein (green) compared to control (black).

CS585 developed as a prostacyclin receptor agonist to inhibit platelet activation and thrombosis

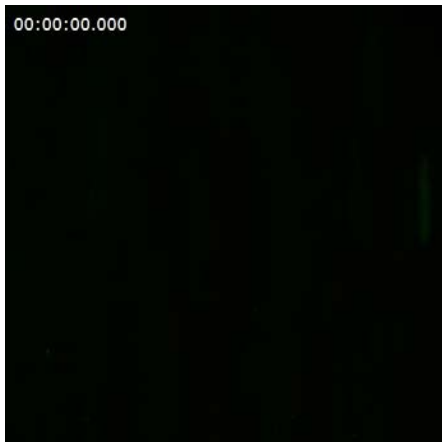
- CS585 selectively targets the IP receptor to inhibit platelet



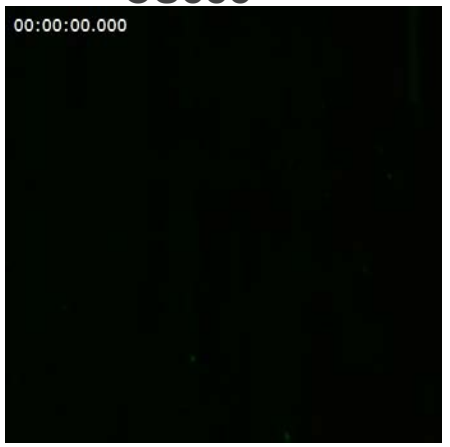




Control

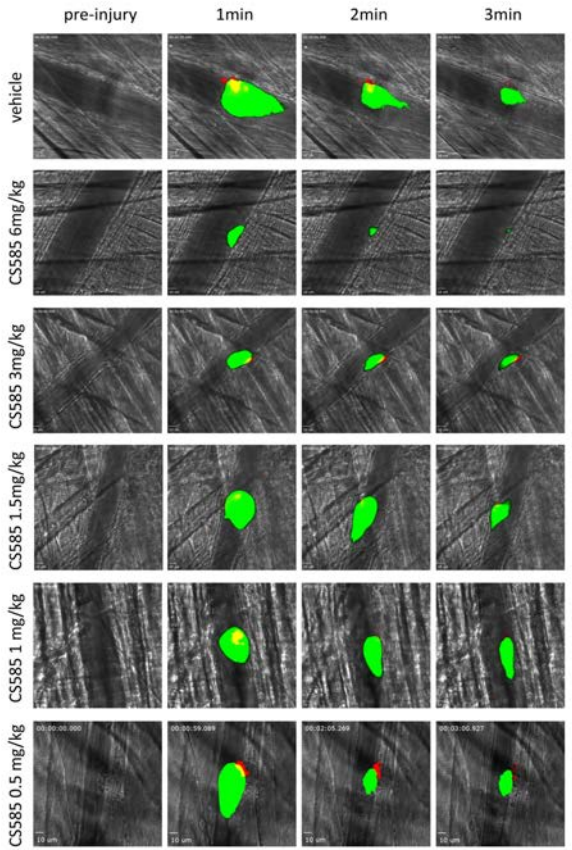


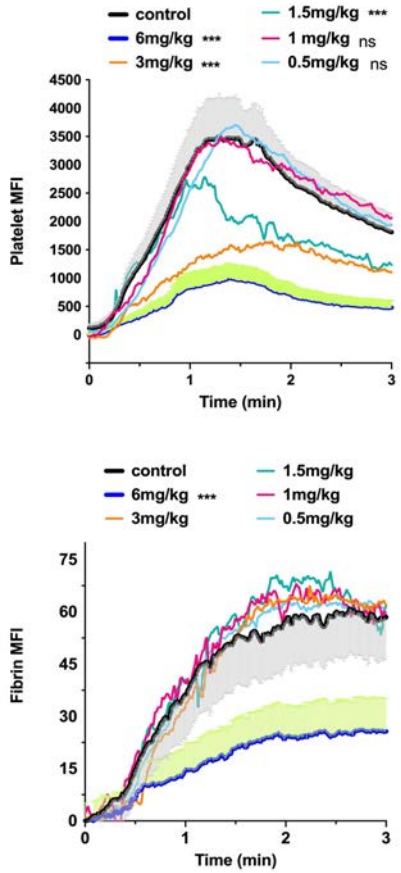
CS585



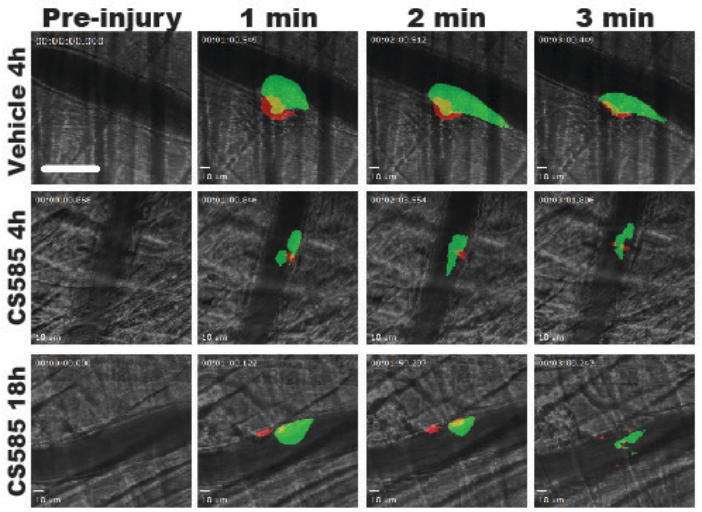
CS585 elicits sustained inhibition of platelet function

Dose-dependent inhibition of thrombus formation:

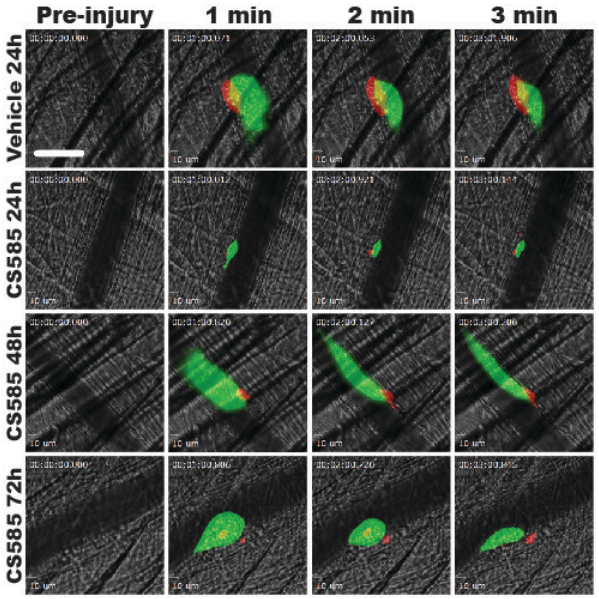




CS585 prevention for over 24 hours

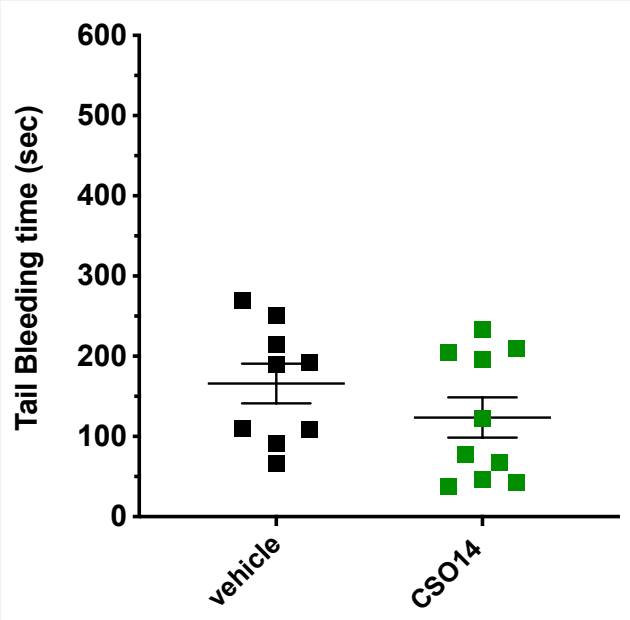


CS585 effects reversible within 48 hours

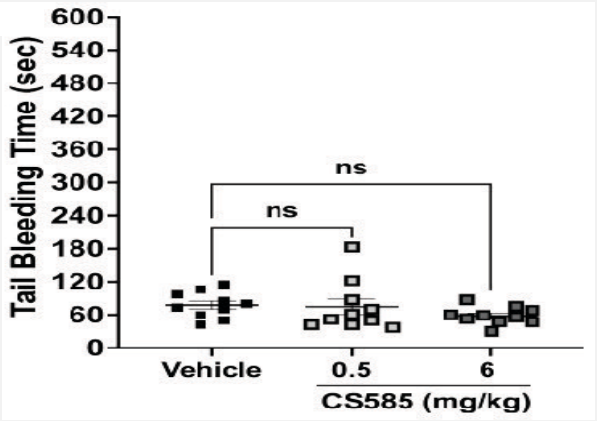


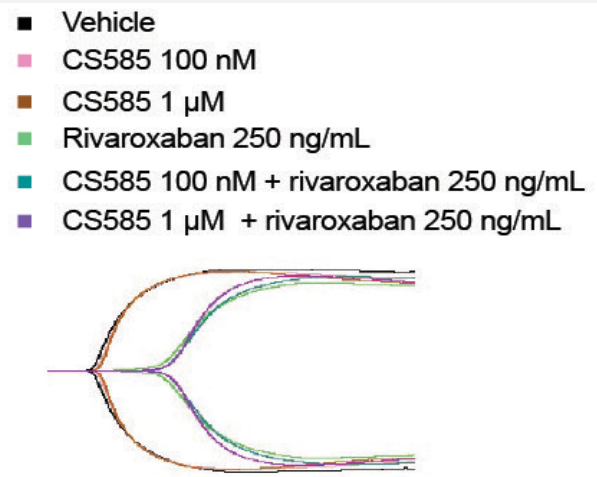
CS014 and CS585 interventions do not increase bleeding risk

CS014



CS585





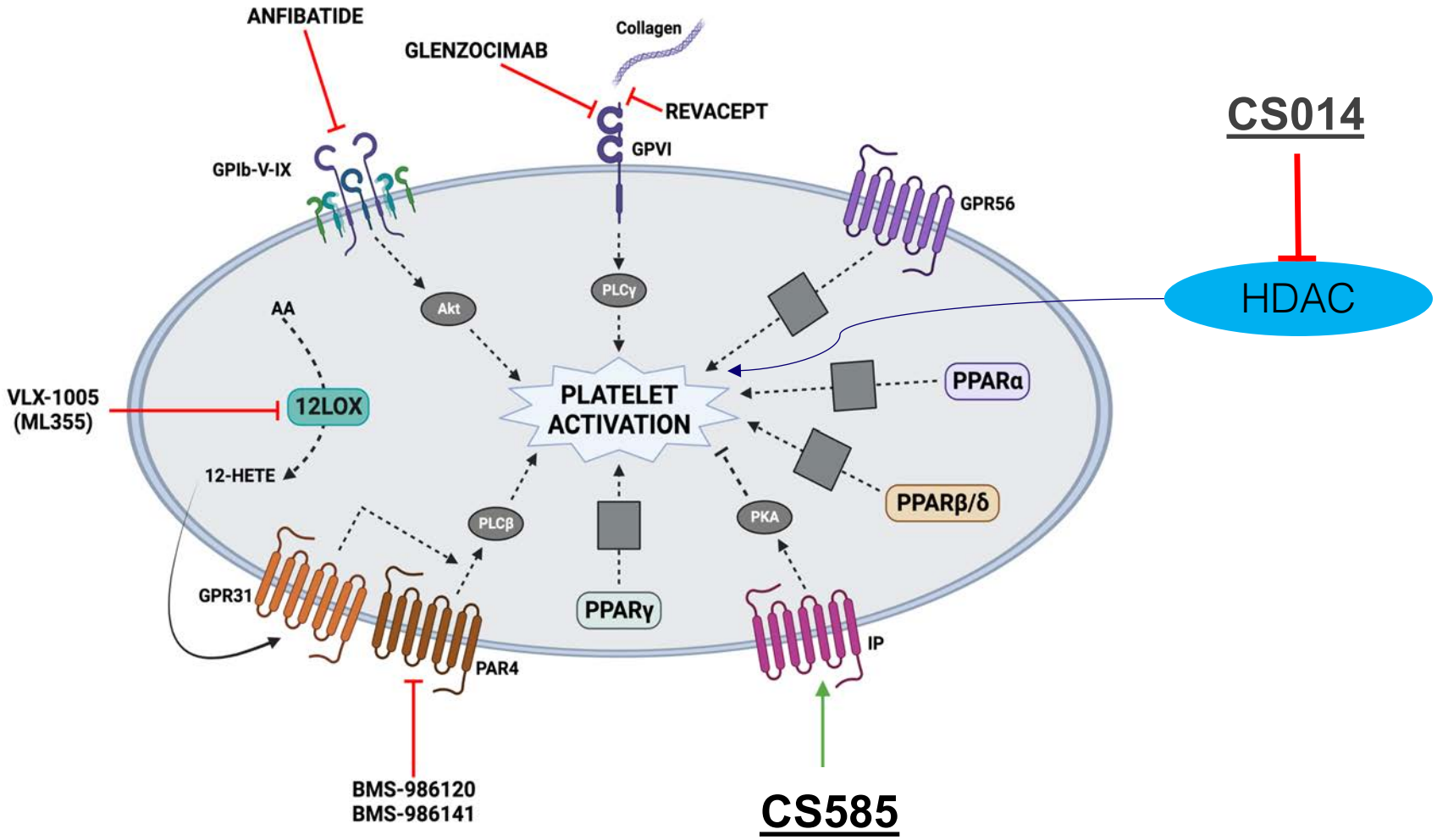
Conclusions:

- **HDACi CS014 inhibits both small and large vessel clotting and fibrin formation**
  - CS014 prevents high shear arterial platelet clot formation and fibrin formation following vascular injury
  - CS014 prevents platelet activation and fibrin formation in low shear conditions following injury

- **CS585 is a novel IP agonist**
  - Stable in human plasma and blood
  - CS585 selectively activates the IP receptor resulting in inhibition of human platelet activation (Human blood)
- CS585 is reversible between 24-48 hours.

- **CS014 and CS585 do not show increased bleeding risk**
- **CS014 and CS585 have significant potential as new approaches to treating thrombosis through inhibition of thrombotic clot formation without the added risk and bleeding.**

Conclusion


ANFIBATIDE
GLENZOCIMAB
Collagen
REVACEPT
GPVI
GPIb-V-IX
GPR56
PLCγ
Akt
AA
VLX-1005
(ML355)
12LOX
12-HETE
PLATELET
ACTIVATION
PPARα
PPARβ/δ
PLCβ
PKA
GPR31
PPARγ
IP
PAR4
BMS-986120
BMS-986141
CS014
HDAC
CS585

Cereno Scientific

Concluding Words

Sten R. Sörensen
Chief Executive Officer (CEO), Cereno

High medical need in thrombosis prevention market - major potential for new effective and safer therapies

Common and rare CVDs result in significant markets due to their high mortality and adverse effect on the quality of life of patients

Societal annual cost of CVD in EU

~ €282 billion
in EU
in 2021

Societal annual cost of CVD in the US

~ $714 billion
In the US
in 2022

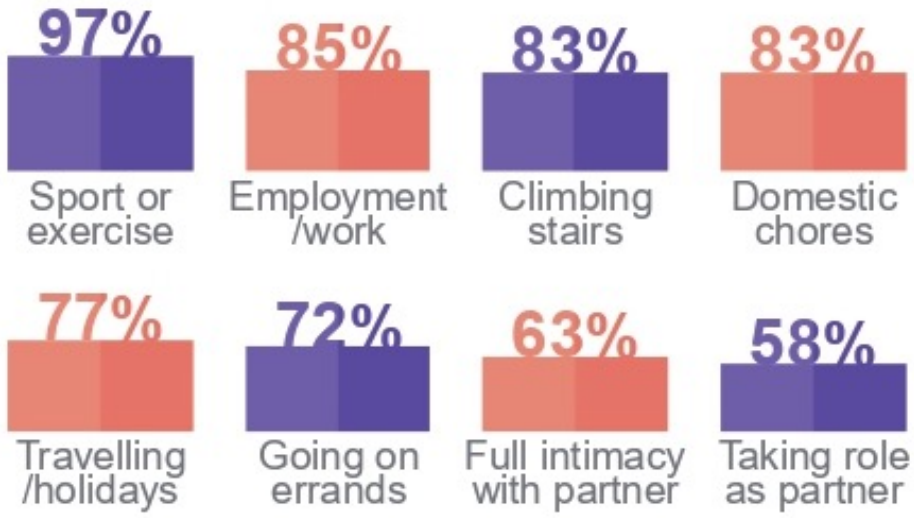
Global anti-thrombotic drug market by 2025 (CAGR 7.5%)

$43.3 Billion

Sources: European Heart Network (link), American Heart Association (link) – 2017 data, Epigenetic Modulation for Cardiovascular Disease. Infogence Global Research (2021) "Global Pulmonary Arterial Hypertension (2021-2027)", MSC Nordics analysis.

High medical need in PAH drug market – major potential for new drugs to increase quality of life and prolong survival

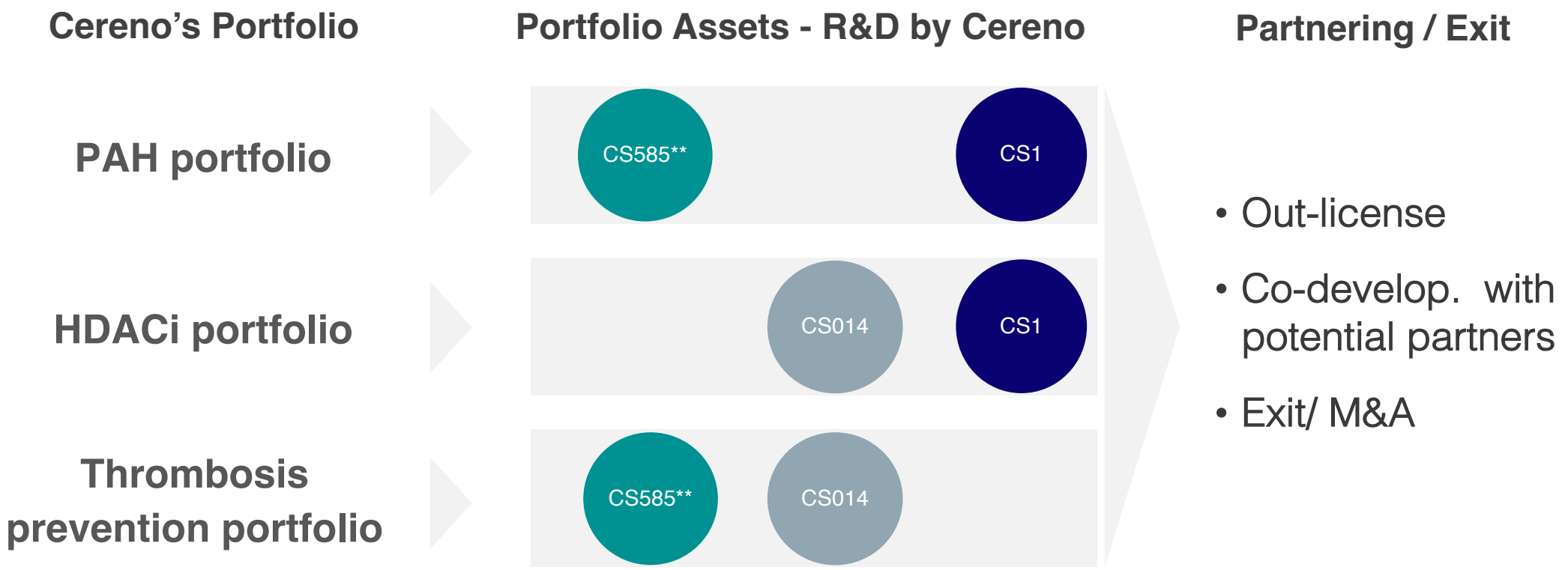
Significant impact on different aspects of patient's lives. A large proportion of PAH patients report difficulties with



Global PAH market by 2027 (CAGR 6.2%)

$11.7 Billion

Cereno develops its pipeline for patients in target indications with high unmet needs to become attractive assets for development with strategic financial/pharma partners or exit through M&A



*Not a chosen target indication. No Indication has been chosen for CS585. It reflects its potential.

Full steam ahead in 2023 and upcoming milestones

Key 2023 achievements

- Company capitalized to progress its R&D programs
- Five patient completed CS1's Phase II study in PAH in collaboration with Abbott
- CS1 patient case data released – data from first patient to complete the CS1's Phase II PAH study
- CS585 published in the top peer-reviewed medical journal "Blood"
- CS585 and CS014 thrombosis data presented at key CVD conferences 2023

Upcoming milestones in 2023 and Q1 2024

- Launching data quality control initiative in CS1 phase II PAH study –Q4'23
- CS014 safety package completion for IND-H2'23
- Topline results for CS1 Phase II PAH study –Q1'24
- CS014 IND submission and initiation of FTIH –H1

Cereno Scientific at ESC 2023

ESC Congress 2023 Amsterdam
Onsite & Online, 25-28 August

Cereno Scientific

Questions from Audience

Cereno Scientific is a clinical-stage biotech company within cardiovascular diseases. The lead drug candidate, CS1, is a Phase II candidate in development for the treatment of the rare disease pulmonary arterial hypertension (PAH). CS1 is an HDAC (histone deacetylase) inhibitor that acts as an epigenetic modulator with pressure-reducing, reverse-remodeling, anti-inflammatory, anti-fibrotic and anti-thrombotic properties, all relevant for PAH. A clinical Phase II study is ongoing to evaluate CS1's safety, tolerability, and efficacy in patients with PAH. A collaboration agreement with global healthcare company Abbott allows Cereno to use their cutting-edge technology CardioMEMS HF System in the study. Cereno also has two promising preclinical drug candidates in development for cardiovascular disease through research collaborations with the University of Michigan. Drug candidate CS014 is a novel HDAC inhibitor with epigenetic effects, selected for prevention of thrombosis as target indication. In preclinical studies it has been documented to regulate platelet activity, fibrinolysis and clot stability for prevention of thrombosis without increased risk of bleeding. Thrombosis prevention in venous or arterial and cardiovascular disease has been selected as the first indication area for CS014. Drug candidate CS585 is a prostacyclin receptor agonist that has been documented in preclinical studies to target the IP receptor for prevention of thrombosis without increased risk of bleeding. The company is headquartered in Gothenburg, Sweden, and has a US subsidiary Cereno Scientific Inc. based in Kendall Square in Boston, Massachusetts, US. Cereno is listed on the Nasdaq First North (CRNO B).

www.cerenoscientific.com