Enhancing and extending lives of people living with diseases with high unmet medical need

Cereno Scientific

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Capital Markets Day 2024

October 17th, 2024 13:30-16:30 CET

Cereno Scientific

Housekeeping

In case of emergency

Agenda

15:05 10-minute break

Q&A – open for questions from audience on site and the web

16:30 Coffee and networking in “Orangeriet”

Speakers

Sten R. Sörensen
Chief Executive Officer

Dr. Björn Dahlöf
Chief Scientific Officer

Dr. Rahul Agrawal
Chief Medical Officer and Head of R&D

Nicholas Oakes
Head of Preclinical Development

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

Dr. Jason Guichard,
Department of Medicine, Division of Cardiology, Prisma Health-Upstate, Assistant Professor of Medicine, University of South Carolina School of Medicine Greenville and investigator in the Phase IIa trial of CS1 in PAH

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

Jan De Backer
CEO, Fluidda

Agenda

Time	Discussion Item	Speaker
13:30	**Welcome**	
13:35	**Introduction to Cereno Scientific**	**Sten R. Sörensen** *CEO, Cereno Scientific*
13:50	**Understanding PAH, a debilitating rare disease**	**Dr. Raymond Benza** *Network Director of Pulmonary Hypertension at Mount Sinai Icahn School of Medicine, New York City*
14:10	**Cereno Scientific's CS1 in PAH**	**Dr. Rahul Agrawal,** *CMO and Head of R&D, Cereno Scientific*
14:15	**Cereno Scientific's CS1 - Phase IIa trial results**	**Dr. Rahul Agrawal,** *CMO and Head of R&D, Cereno Scientific* **Nicholas Oakes,** *Head of Preclinical Development, Cereno Scientific*
14:40	**Investigator and patient perspective of CS1-003 trial**	**Dr. Jason Guichard** *Cardiologist at Prisma Health-Upstate, Assistant Professor of Medicine, University of South Carolina School of Medicine Greenville and investigator in the Phase IIa trial of CS1 in PAH*

Time	Discussion Item	Speaker
14:45	**Next steps for CS1**	**Dr. Rahul Agrawal** *CMO and Head of R&D, Cereno Scientific*
14:55	**Introduction to Fluidda and the innovative Functional Respiratory Imaging technology**	**Jan De Backer** *CEO Fluidda*
15:05	**Short break**	
15:15	**CS014 targeting unmet needs in rare disease IPF**	**Dr. Björn Dahlöf**, *CSO, Cereno Scientific*
15:35	**CS585 being evaluated rare diseases**	**Dr. Michael Holinstat** *Prof. at University of Michigan Medical School; and Director Translation Research, Cereno Scientific*
15:55	**Cereno Scientific - strategic priorities and future outlook**	**Sten R. Sörensen** *CEO, Cereno Scientific*
16:10	**Questions from Audience on site and online**	Moderated by Dr. Rahul Agrawal, *CMO and Head of R&D, Cereno Scientific*
16:25	**Concluding remarks**	**Sten R. Sörensen** *CEO, Cereno Scientific*

Sten R. Sörensen
Chief Executive Officer

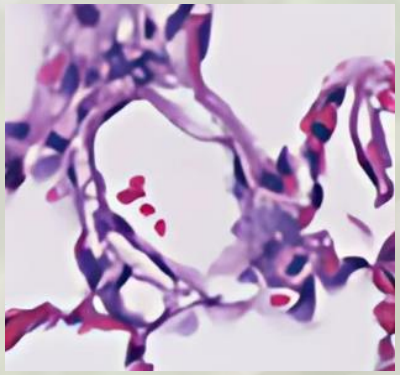
Introduction to Cereno Scientific

Cereno Scientific

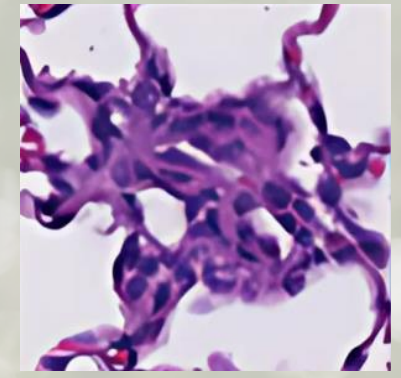
Disclaimer

CS1-003 is a phase IIa trial that is not powered for statistically significant detection of efficacy-related parameters. This presentation has been prepared and produced by Cereno Scientific AB (publ) ("Cereno Scientific") solely for Cereno Scientific's investor presentation and may not be used for any other purpose. Unless otherwise stated, Cereno Scientific is the source for all data contained in this presentation. Such data is provided as at the date of this presentation and is subject to change without notice. This presentation includes forward-looking statements. These forward-looking statements involve known and unknown risks, uncertainties and other factors, which may cause Cereno Scientific's actual results, performance, achievements or industry results to be materially different from those expressed or implied by these forward-looking statements. Forward-looking statements speak only as of the date of this presentation and Cereno Scientific expressly disclaims any obligation or undertaking to release any update of, or revisions to, any forward-looking statement in this presentation, as a result of any change in Cereno Scientific's expectations or any change in events, conditions or circumstances on which these forward-looking statements are based. This presentation does not constitute or form part of, and should not be construed as, an offer or invitation for the sale of or the subscription of, or a solicitation of any offer to buy or subscribe for, any securities, nor shall it or any part of it or the fact of its distribution form, or be relied on in connection with, any offer, contract, commitment or investment decision relating thereto, nor does it constitute a recommendation regarding the securities of Cereno Scientific. The information in this presentation has not been independently verified. No regulatory body in Sweden or elsewhere has examined, approved or registered this presentation.

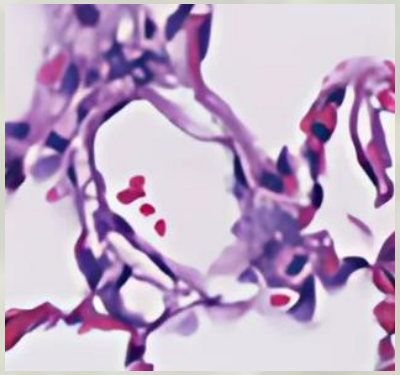
Healthy pulmonary artery



Plexiform Lesions in PAH



Healthy pulmonary artery



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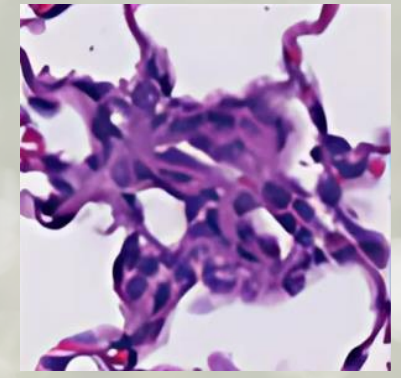
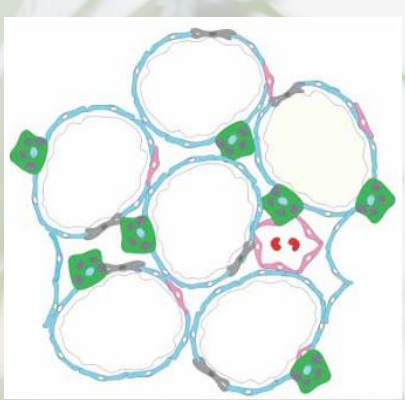
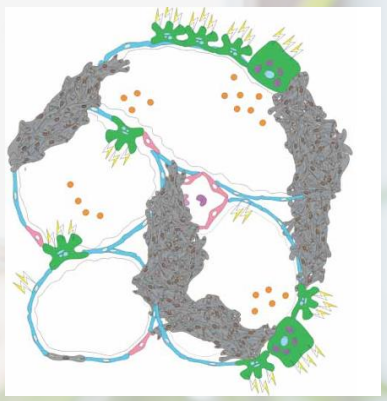


What if…

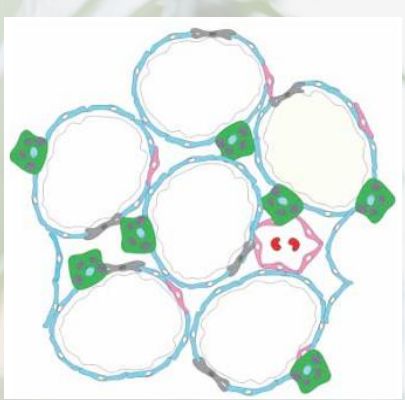
Healthy



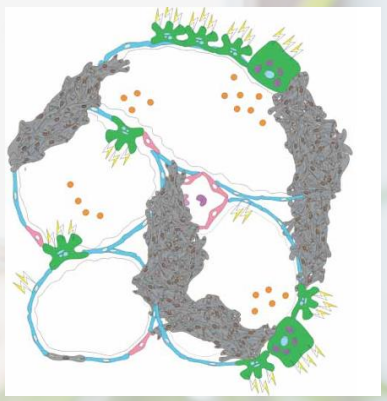
IPF Lung



Healthy



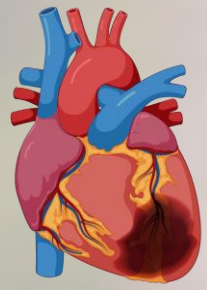
IPF Lung



What if…

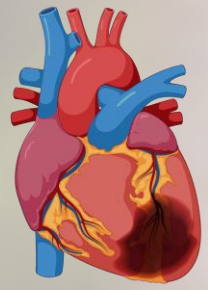
Stroke

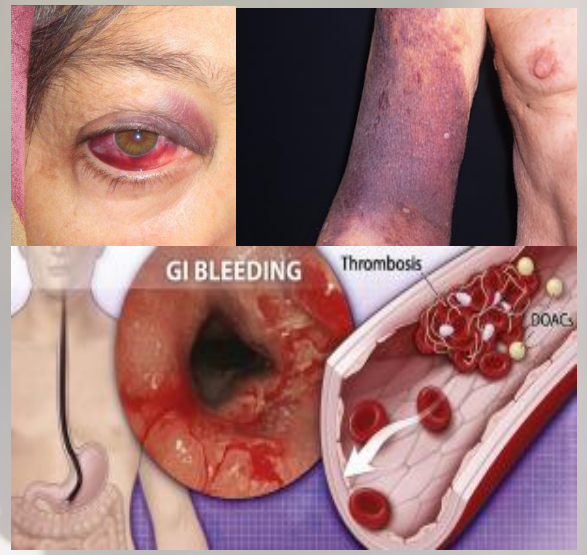
Cardiac thrombosis



Stroke

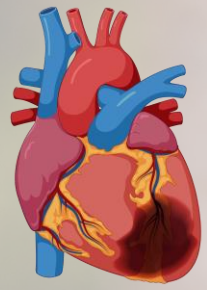
Cardiac thrombosis

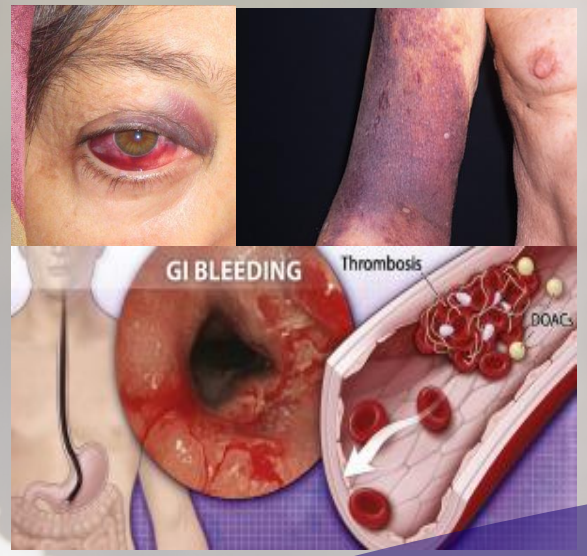




Stroke

Cardiac thrombosis



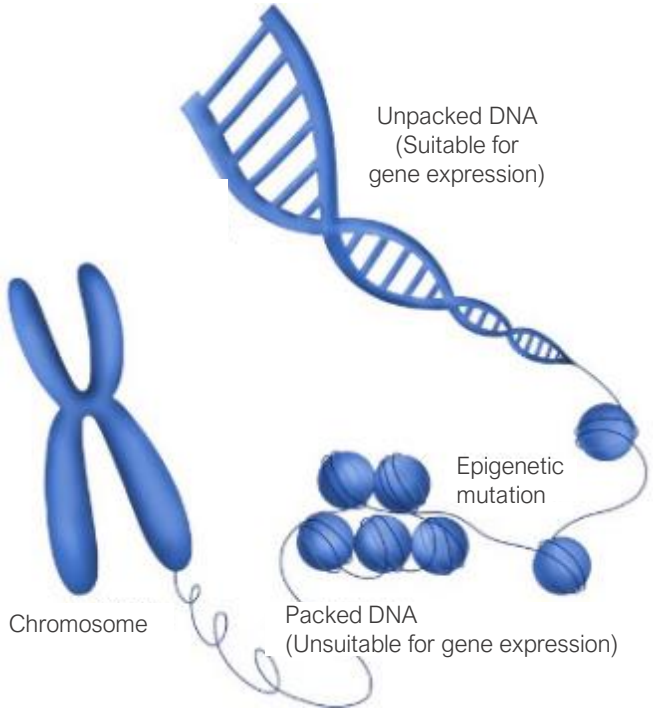


What if…

Cereno develops innovative treatments for diseases with high unmet medical needs

Cereno's HDACi portfolio is untapping the potential of epigenetic modulation in CVD

- Histone deacetylase inhibition (HDACi) plays important role in epigenetic modulation.[1-14]
- Epigenetic modulation - alteration of gene expression without altering genetic material.[1,2]



Disease-modifying elements of CVD addressed by HDACi

1. Reverse pathological remodeling
2. Anti-fibrotic
3. Anti-inflammatory
4. Pulmonary pressure reduction
5. Anti-thrombotic (fibrinolytic, anti-platelet)

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Source:1. Ferreira JP, Pitt B, and Zannad F, Lancet Healthy Longev 2021;2,e371-379; 2. Bisserier M. et.al. Vasc Biol. 2020 Jan;2(1):R17-R34. 3. Duenas-Gonzales, A., et al, 2008, Link; 4. Han, W., et al, 2021, Link; 5. Kabel, A., et al, 2016, Link; 6. Lan, B., et al, 2015, Link; 7. Zhao, L., et al, 2012, Link; 8. Cardinale, J., et al, 2010, Link; 9. Costalonga, E., et al, 2017, Link; 10. Seet, L., et al, 2019, Link; 11. Wu, S., et al, 2015, Link; 12. Larsson, P., et al, 2016, Link; 13. Saluveer, O., et al, 2014, Link; 14. Svennerholm, K., et al, 2015, Link.

Cereno's portfolio is uniquely positioned to make impact in diseases with high unmet medical needs

Program	Target	Indication	Preclinical	Phase I	Phase II	Phase III	Status
CS1	HDACi with disease-modifying potential	PAH					Phase II top-line results in Q3 2024[1] Expanded Access Program initiated in Q1 2024[1]
CS014	HDACi with disease-modifying potential	IPF					Phase I initiated in Q2 2024[2]
CS585	PRA oral, selective and potent	CVD					Ongoing preclinical development during 2024/25

Note: Progress bars are only an estimation, not to scale.

Source: 1. Cereno Press Release, 21st Feb 2024; 2. Cereno Press Release, 18th June 2024

Pipeline attractive for strategic financial & pharma partners

Cereno's assets/portfolio for:

- Co-development
- Out-licensing
- Asset trade sale
- M&A
- Commercialization

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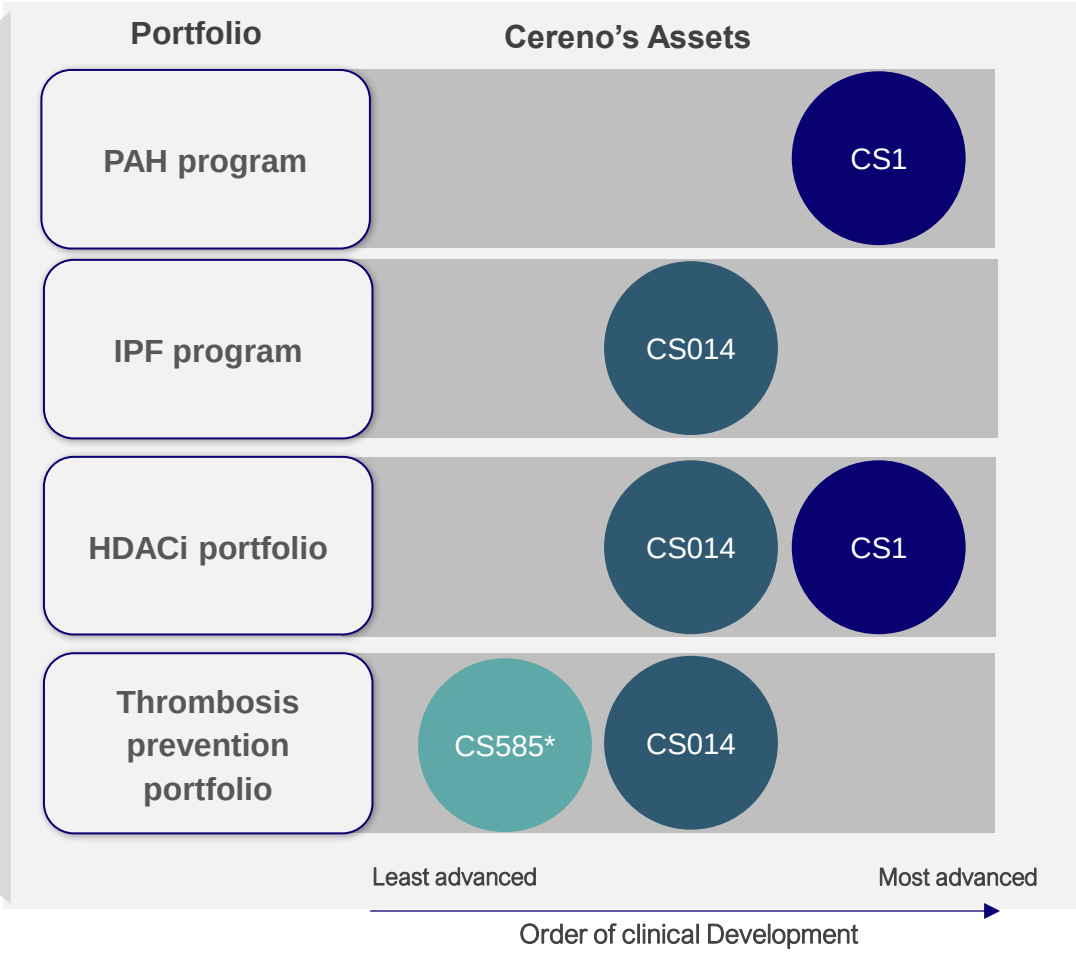


*No Indication has been chosen for CS585. It reflects its potential.

Cereno develops innovative treatments for diseases with high unmet medical needs

Pioneering epigenetic modulation through HDAC inhibition (HDACi) with disease-modifying potential in CVD

Pipeline portfolio:

CS1: Phase IIa HDACi completed, ODD in PAH

CS014: Phase I HDACi ongoing, target indication IPF

CS585: Preclinical prostacyclin receptor agonist (PRA)

Lead program CS1 completed Phase II (USA) in PAH with positive topline data

FDA-approved CS1 Expanded Access Program initiated – Q1 2024

Cereno's global presence

HQ: Gothenburg, Sweden

US subsidiary: Boston, MA

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

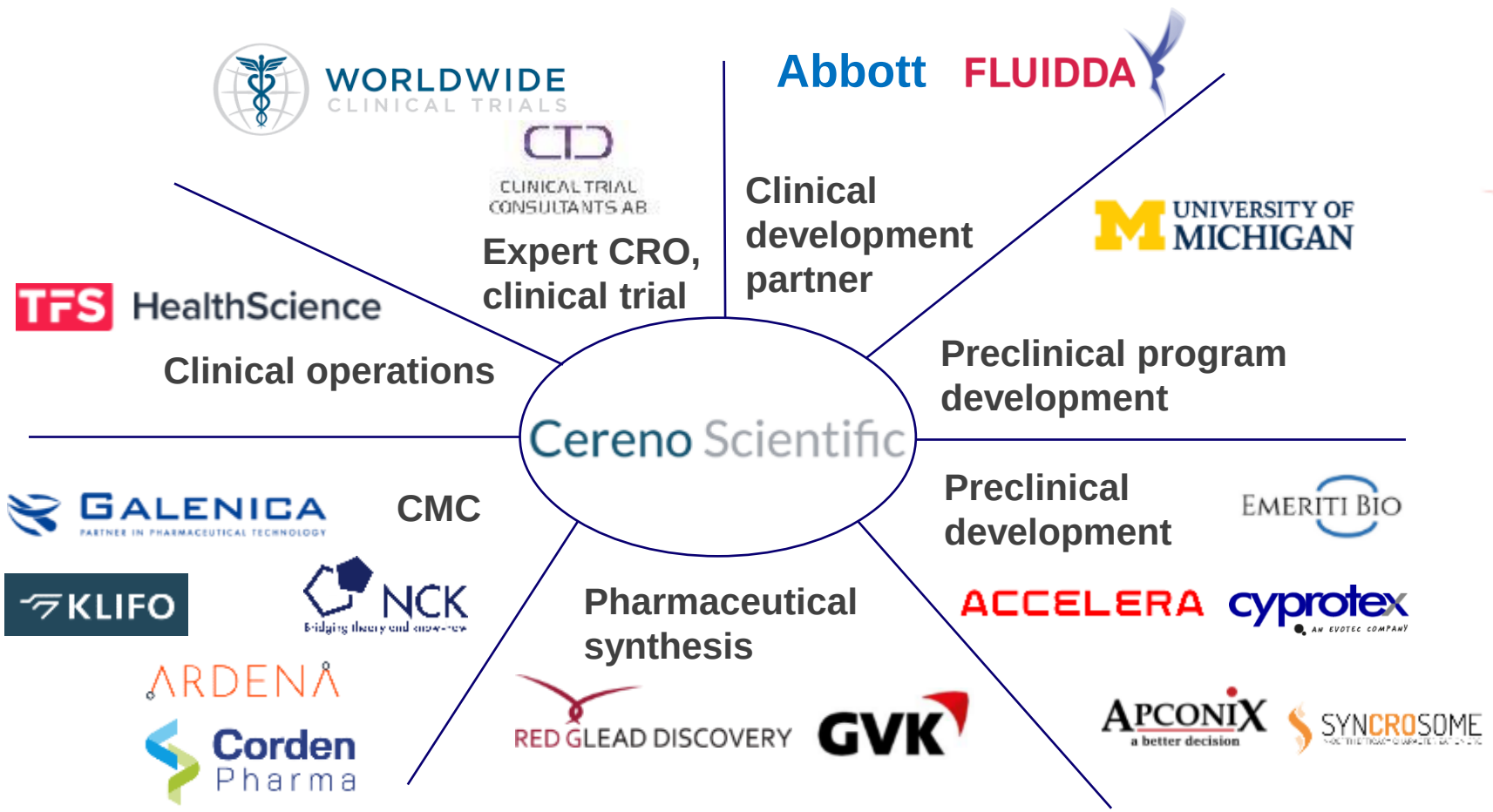
Preclinical R&D collaboration: University of Michigan, MI

Listed on Nasdaq First North Growth Market (CRNO B)

CVD – Cardiovascular Diseases, HDAC- Histone Deacetylases, ODD- Orphan Drug Designation, PAH – Pulmonary Arterial Hypertension

Cereno Scientific Head Quarters @ GoCo Health Innovation City
Gothenburg, Sweden

Global network of world-leading experts



Regulatory strategy

Regulatory strategy

US regulatory strategy

IPR strategy

IPR strategy

Scientific communications

Regulatory

Pricing and Access

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

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

Understanding PAH: a debilitating rare disease

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New Medications are Needed 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

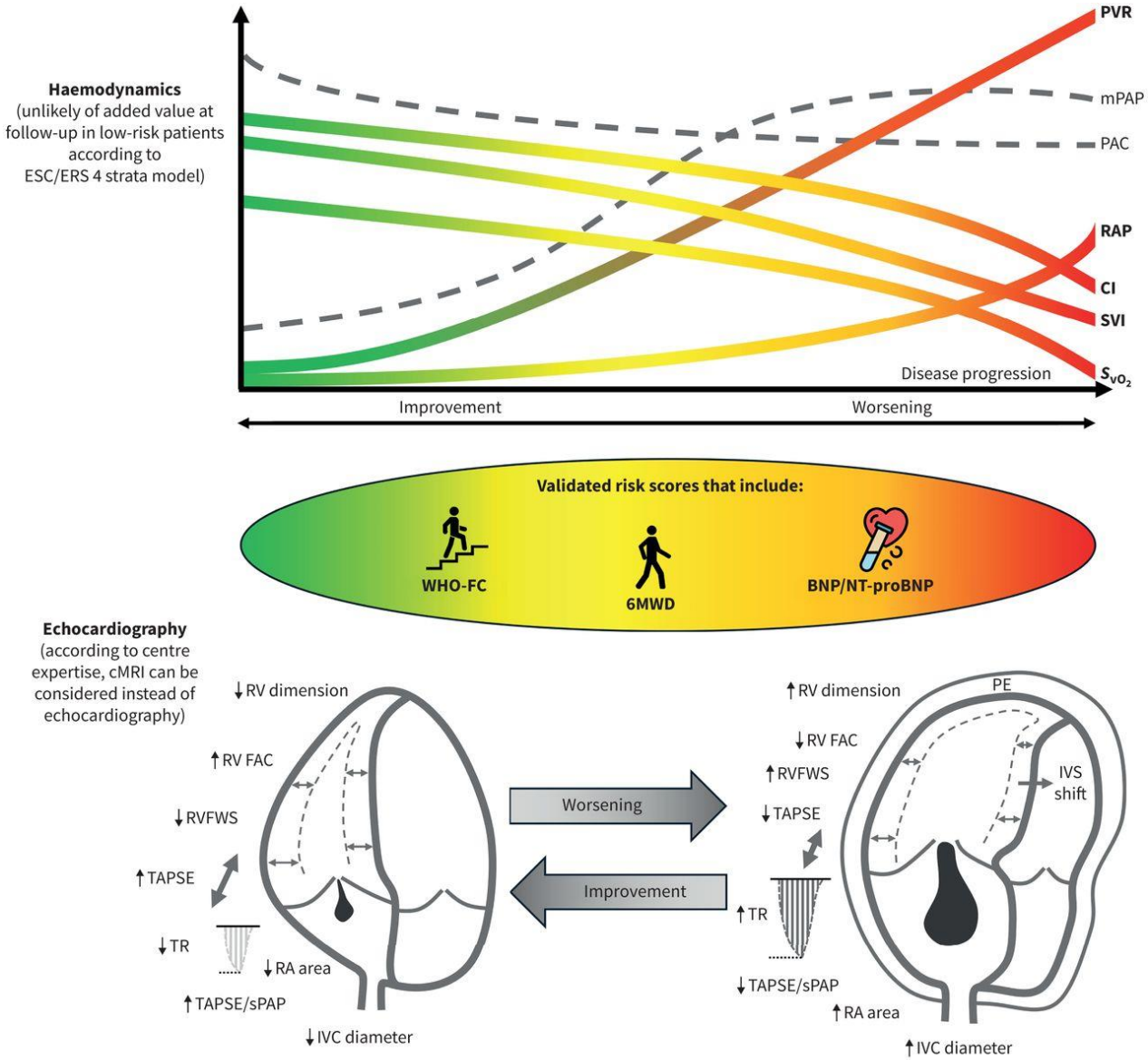
Icahn School of Medicine at Mount Sinai

The Missing Links in Contemporary Drug Therapy

1: Nonguideline adherence to therapeutic utilization
2. Non utilization of prognostic tools to guide therapy
3. Poor access to current medications
4. Lack of vascular targeting of current therapeutics

Icahn School of Medicine at Mount Sinai

Multidimensional Strategy for Risk Stratification and Management Decisions in PAH



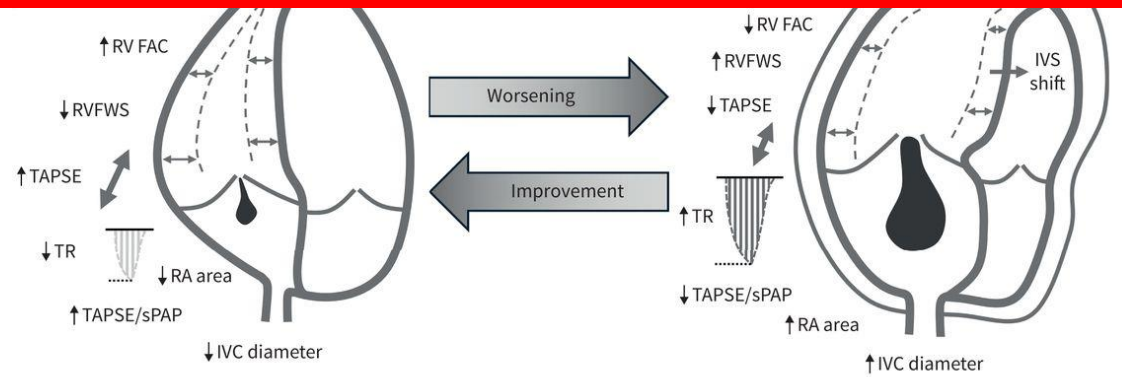
In grey: risk determinants with a less well-defined role as treatment goals

Fabio Dardi et al. Eur Respir J doi:10.1183

Multidimensional Strategy for Risk Stratification and Management Decisions in PAH

Achievement of a Low-Risk Status defined as

< 5% mortality at 1 year



In grey: risk determinants with a less well-defined role as treatment goals

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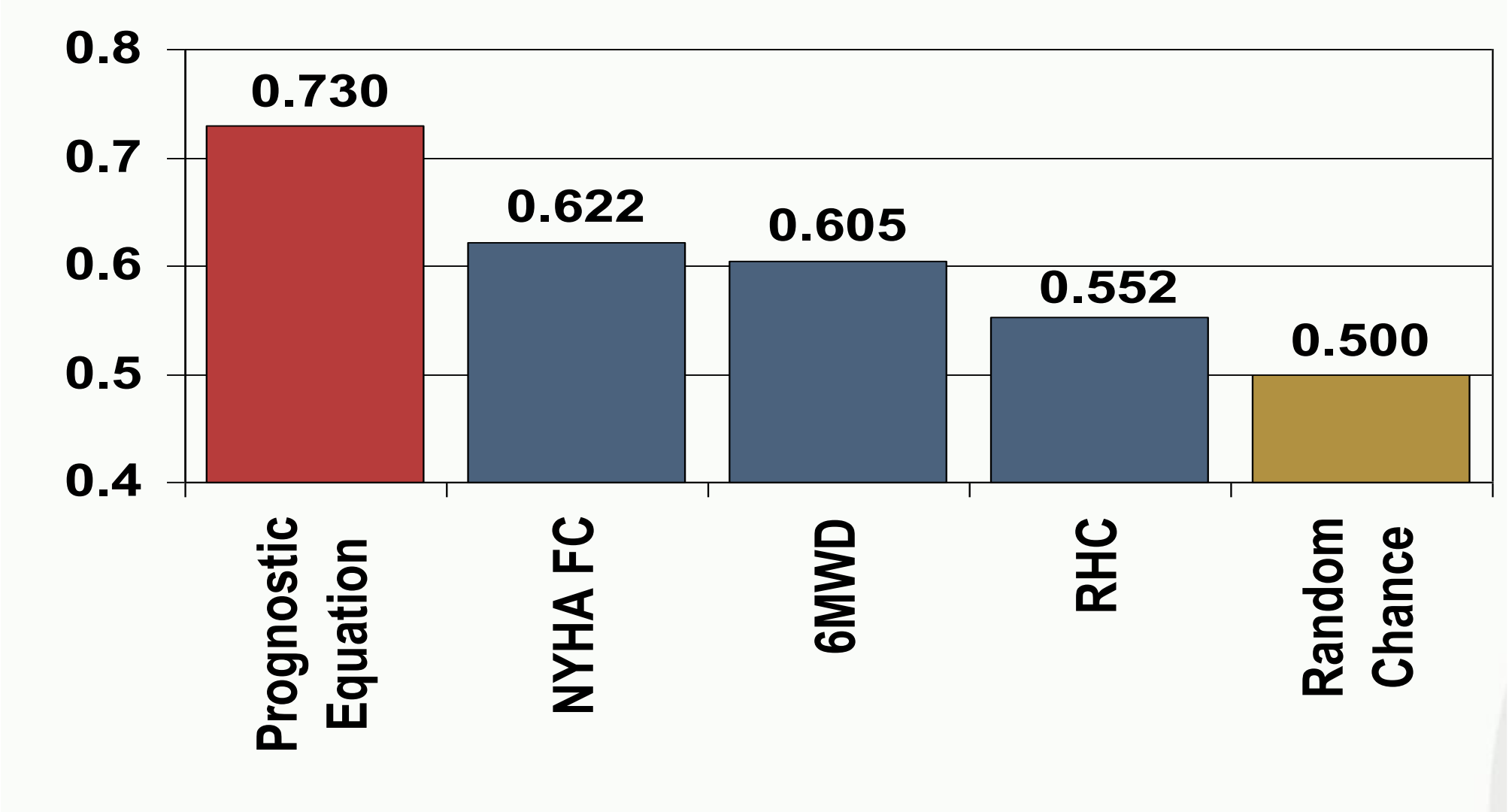
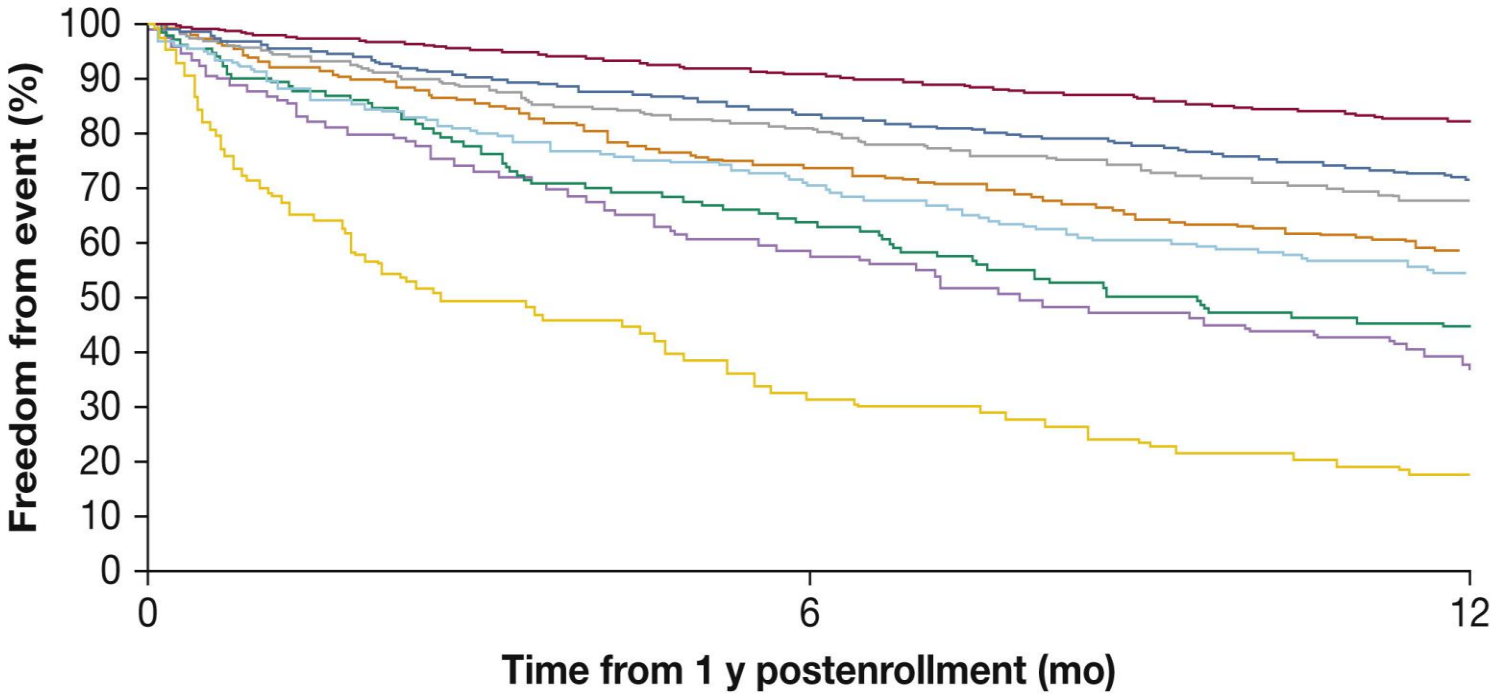
Assessing Discrimination: One Test doesn't Tell it All

C-Indices for commonly used single variables vs a Prognostic Equation



Registry to[A] ertension

WHO group 1 subgroup
Male >60 years
All-cause hospitalisation ≤6 months
eGFR <60 mL/min/1.73m² or renal insufficiency
Systolic BP (mmHg)
Heart rate (bpm)
WHO-FC
6MWD (m)
BNP (ng·L⁻¹) or NT-proBNP (ng·L⁻¹)
PE on echocardiogram
D_{LCO} ≤40 % pred
RAP >20 mmHg within 1 year
PVR <5 WU



	No. at risk		
Score = 0-6	1,073	963	864
Score = 7	386	314	262
Score = 8	306	245	200
Score = 9	266	192	149
Score = 10	195	134	102
Score = 11	130	82	55
Score = 12	90	52	34
Score = 13+	83	26	13

Overall

1	2
Yes	
<110	
>95	
III	IV
<165	
200–800	≥800
	≥1100

risk
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used as a
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ne of risk

Score = 0-6 — Score = 7 — Score = 8 — Score = 9
Score = 10 — Score = 11 — Score = 12 — Score = 13+

Fabio Dardi et al. Eur Respir J

Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) risk tools.

REVEAL 2.0

	−2	−1	0	1	2	3
WHO group 1 subgroup			Other	CTD	Heritable	PoPH
Male >60 years			No		Yes	
All-cause hospitalisation ≤6 months			No	Yes		
eGFR <60 mL/min/1.73m² or renal insufficiency			No	Yes		
Systolic BP (mmHg)			≥110	<110		
Heart rate (bpm)			≤95	>95		
WHO-FC		I	II	III	IV	
6MWD (m)	≥440	320–440	165–320	<165		
BNP (ng·L⁻¹) or NT-proBNP (ng·L⁻¹)	<50 <300		50–200 300–1100	200–800	≥800 ≥1100	
PE on echocardiogram			No	Yes		
D_{LCO} ≤40 % pred			No	Yes		
RAP >20 mmHg within 1 year			No	Yes		
PVR <5 WU		Yes	No			

Overall risk= sum of the points +6 =
- 0–6= Low risk
- 7–8= Intermediate risk
- ≥9= High risk

REVEAL Lite 2

	−2	−1	0	1	2
eGFR <60 mL/min/1.73m² or renal insufficiency			No	Yes	
Systolic BP (mmHg)			≥110	<110	
Heart rate (bpm)			≤95	>95	
WHO-FC		I	II	III	IV
6MWD (m)	≥440	320–440	165–320	<165	
BNP (ng·L⁻¹) or NT-proBNP (ng·L⁻¹)	<50 <300		50–200 300–1100	200–800	≥800 ≥1100

Overall risk= sum of the points +6 =
- 0–5= Low risk
- 6–7= Intermediate risk
- ≥8= High risk

REVEAL is meant to be used as a continuous score not categorial or strata: Allows multiple line of risk

Fabio Dardi et al. Eur Respir J doi:10.1183/13993003.01323-2024 Benza R: Chest. 2019 Aug;156(2):323-337.

Advantages of Continuous Risk

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

Freedom EV: 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: 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: 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: REVEAL 2.0 for every a 1-point decrease in RRS 2.0 at PATENT-1 Week 12 was associated with a 26% reduction in the relative risk of death and a 23% reduction in the relative risk of clinical worsening in PATENT-2

The Missing Link in Contemporary Drug Therapy

1: Survival and Morbidity is still too High
2. Target Disease Effect: Vasodilation vs Remodeling
3. Lack of specific Tissue Targeting
4. Systemic Side Effects
5. Persistent Dependency of Parenteral Therapy

Icahn School of Medicine at Mount Sinai

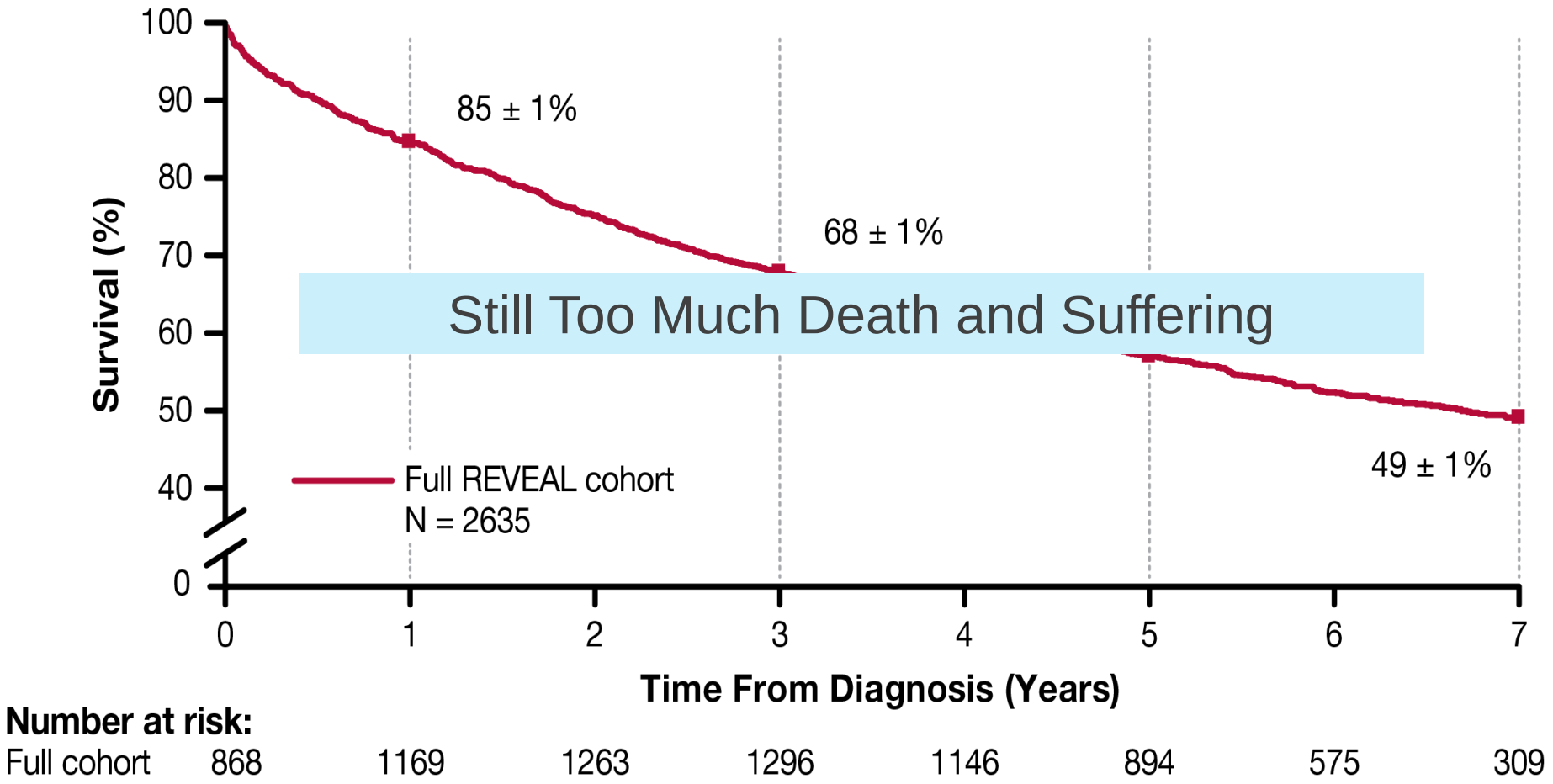
Event free Survival and QOL in Pulmonary Hypertension:

Is it Where We Want it to be with Contemporary Therapy??

Icahn
School of
Medicine at
Mount
Sinai

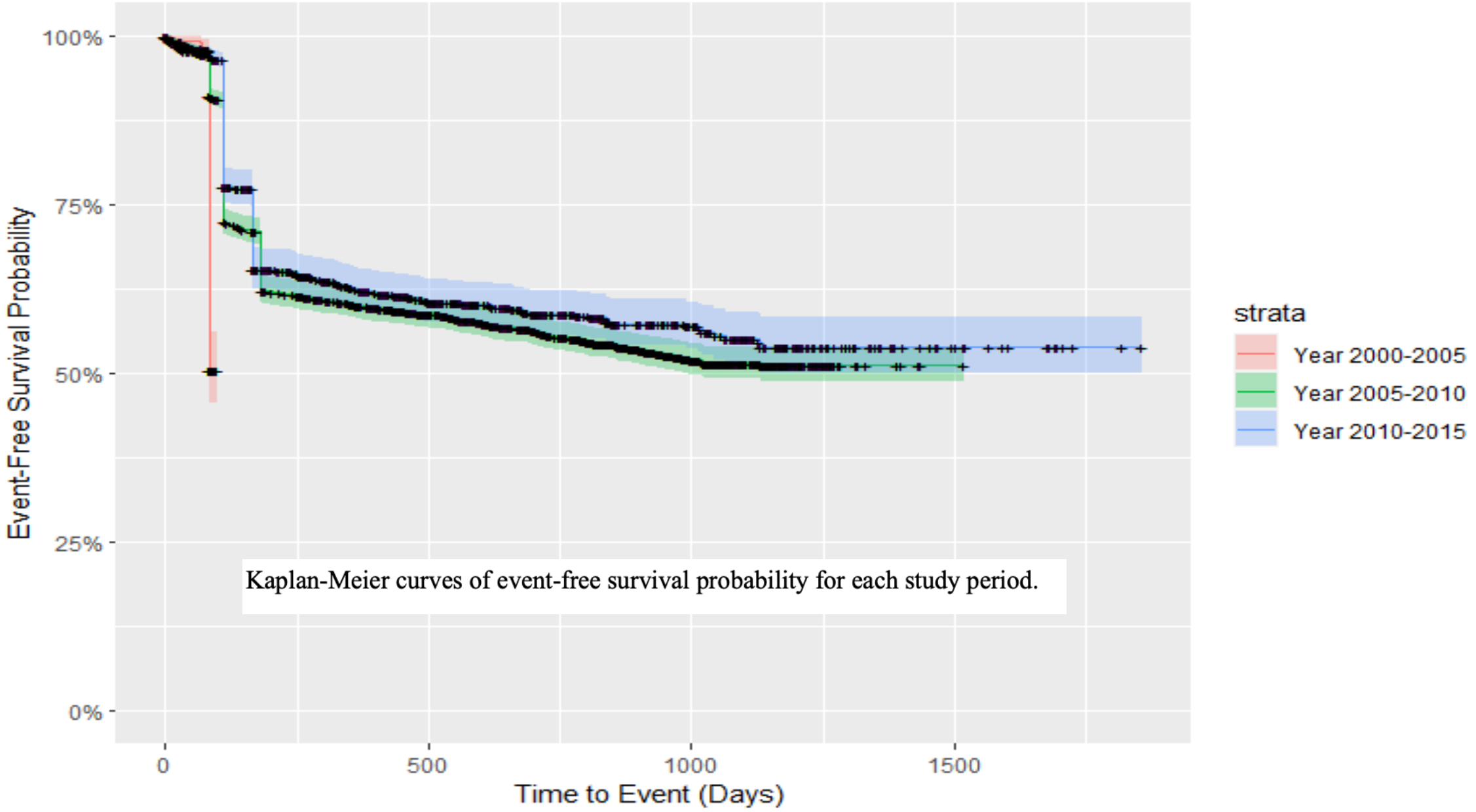
Pulmonary Arterial Hypertension: Long term Survival

Benza RL *et al. Chest* 2012; 142:448–56.



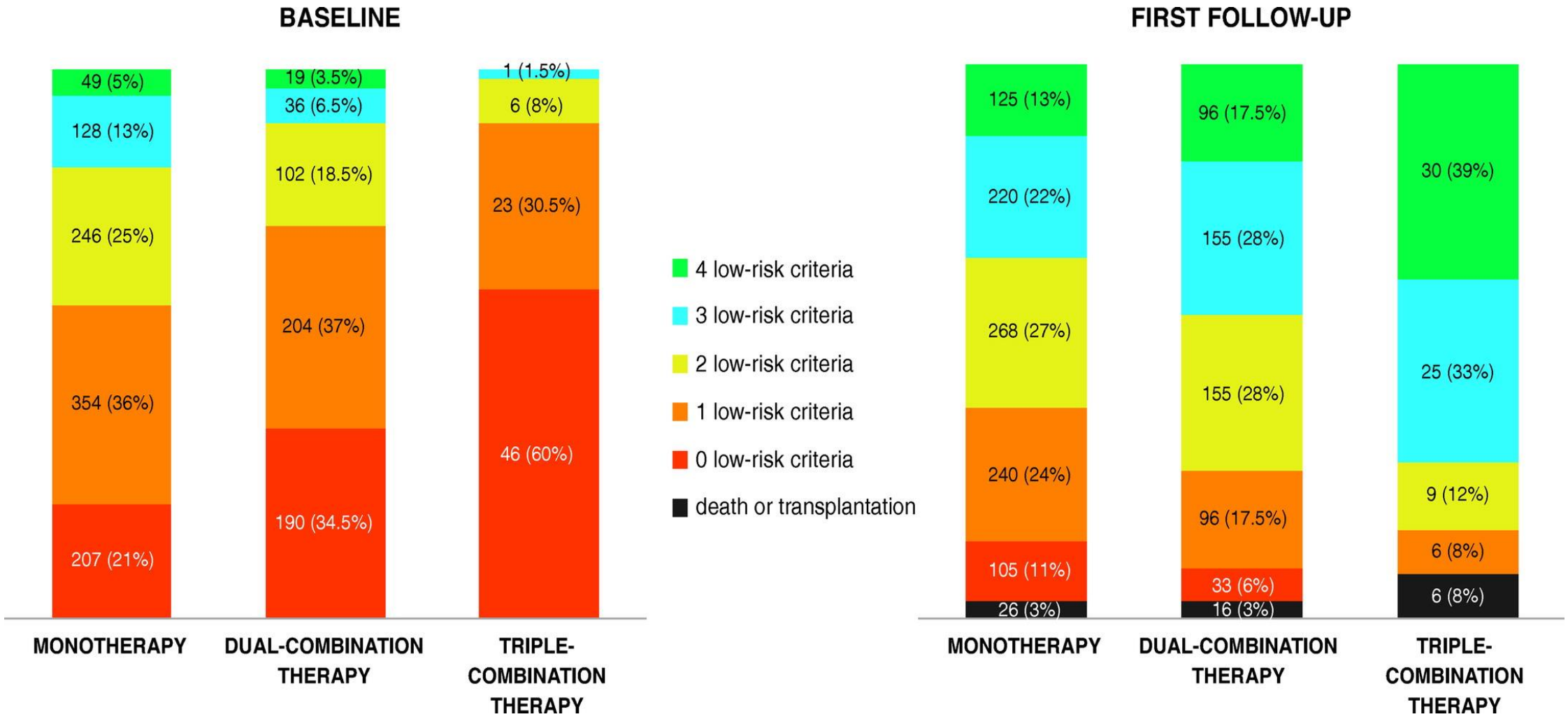
- Long-term data → observational registries
- Median survival has increased ~ 7 vs 3 years in the 80s
- Still, 7 year survival rate is unacceptable
- Morbid events now outrank mortal events and these predict future events (Mortal and Morbid)

No Meaningful Changes in Morbid Events Over the Past 2 Decades



Kaplan-Meier curves of event-free survival probability for each study period.

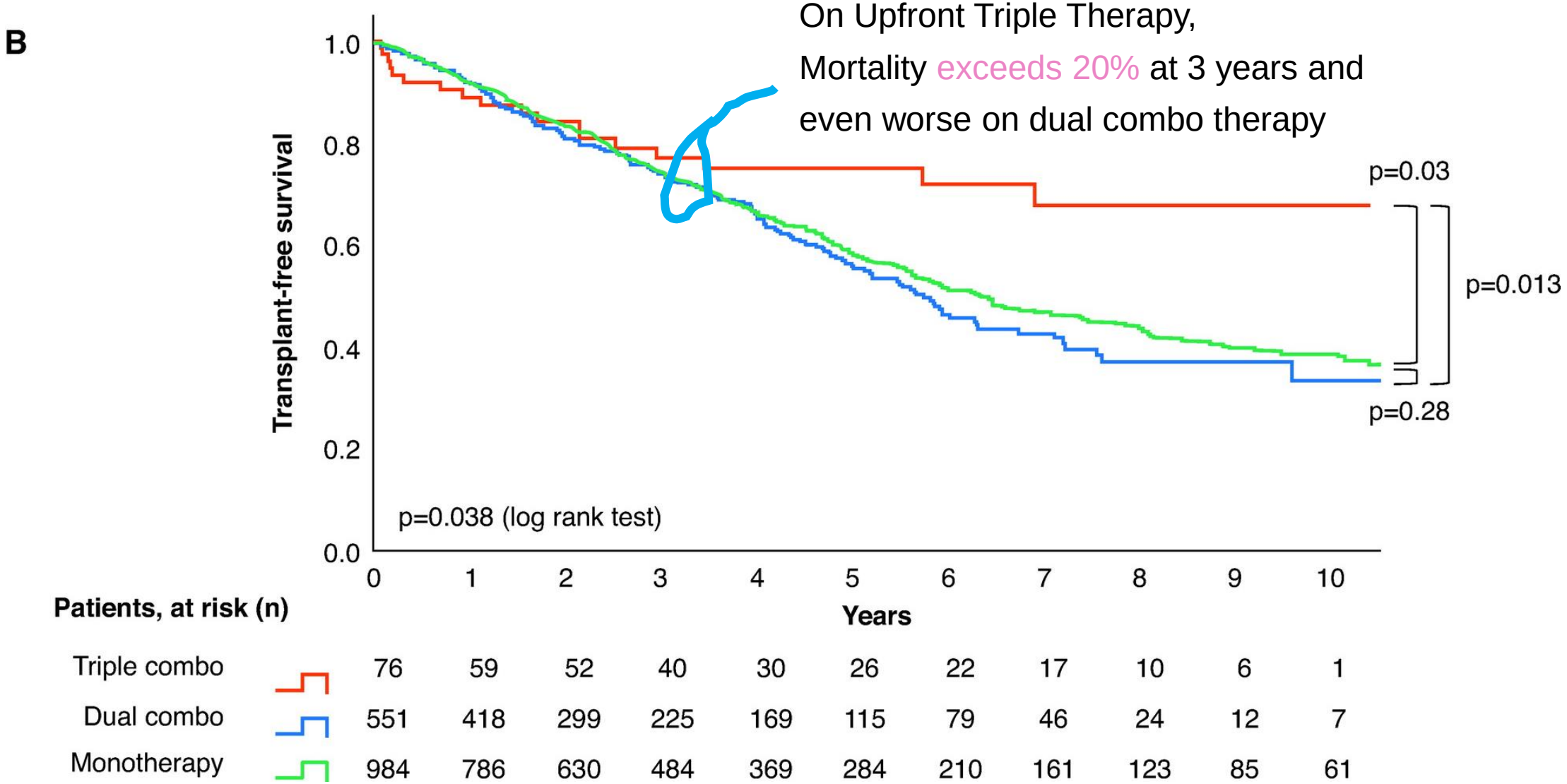
If We Don't Throw the Kitchen Sink at our Patients All at Once….. >50% will Stay at Higher Risk



Boucly a,…Sitbon O Am J Respir Crit Care Med 204842-854. DOI: 10.1164/rccm.202009-3698OC

Mortality still Unacceptable on the Best and Most Aggressive Contemporary PAH Therapy

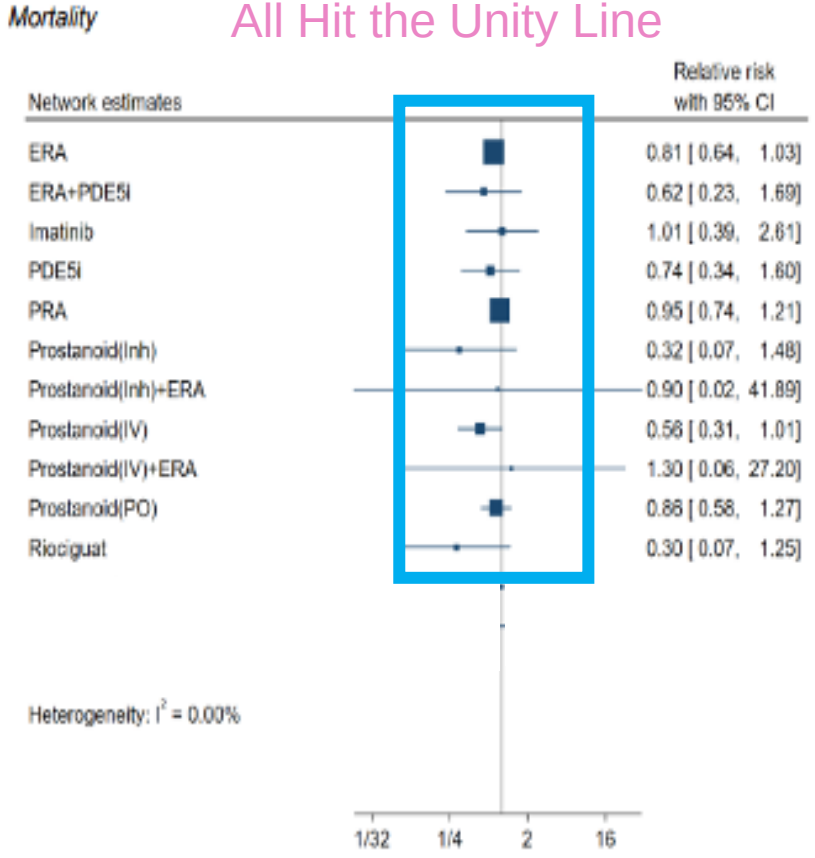
On Upfront Triple Therapy,
Mortality exceeds 20% at 3 years and
even worse on dual combo therapy

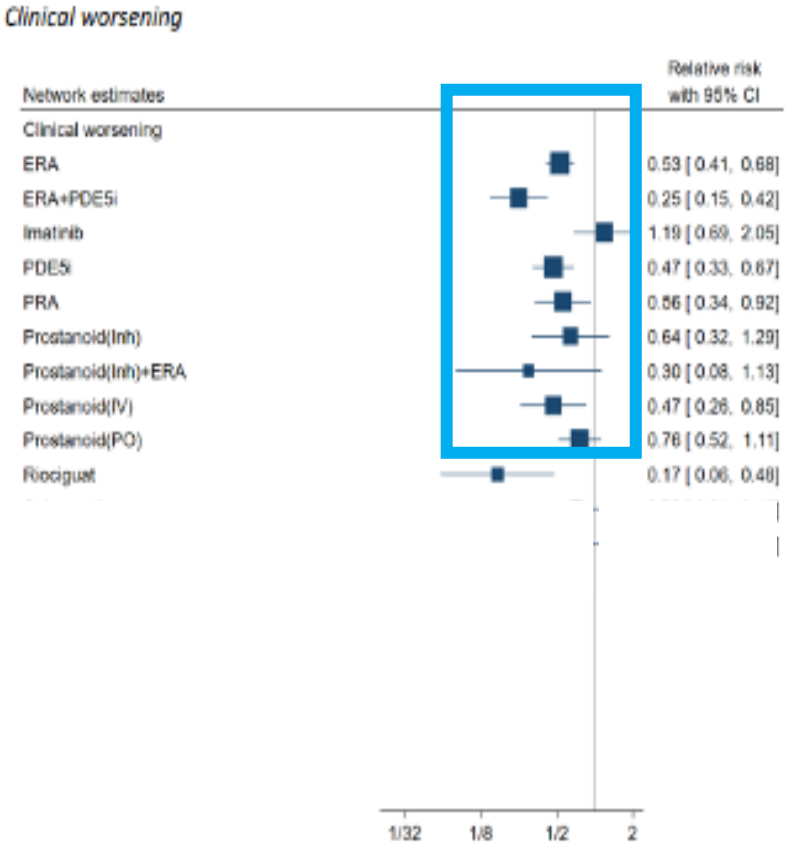


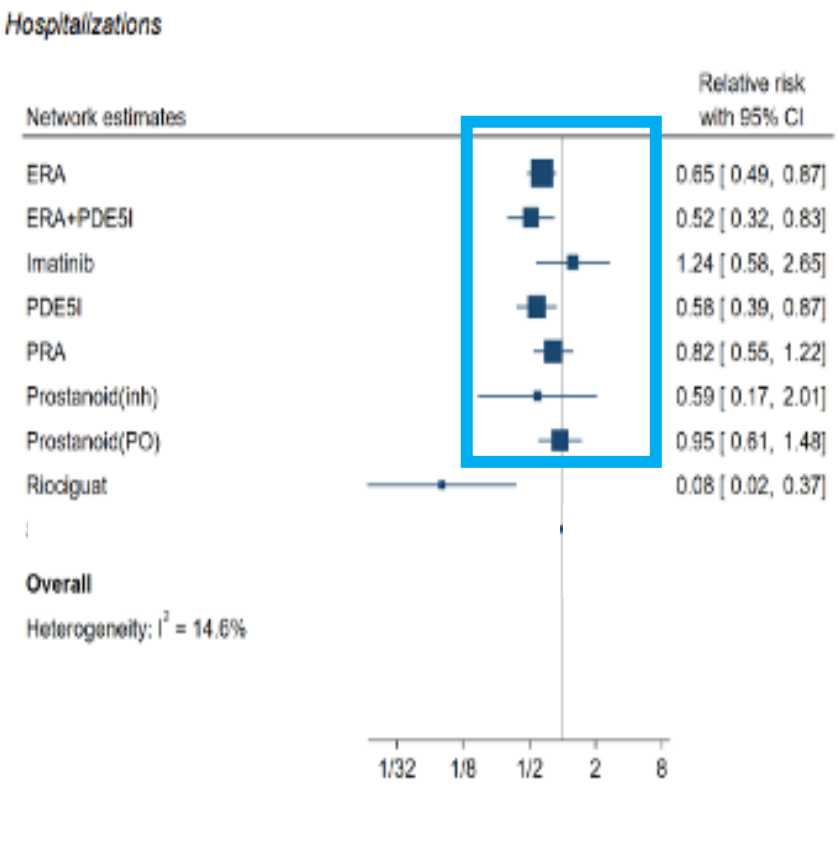
Boucly a,…Sitbon O Am J Respir Crit Care Med 204842-854. DOI: 10.1164/rccm.202009-3698OC

Medications for the Treatment of Pulmonary Arterial Hypertension: A Systematic Review and Network Meta-Analysis

All Hit the Unity Line







Pitre, T European Respiratory Review 2022 31: 220036

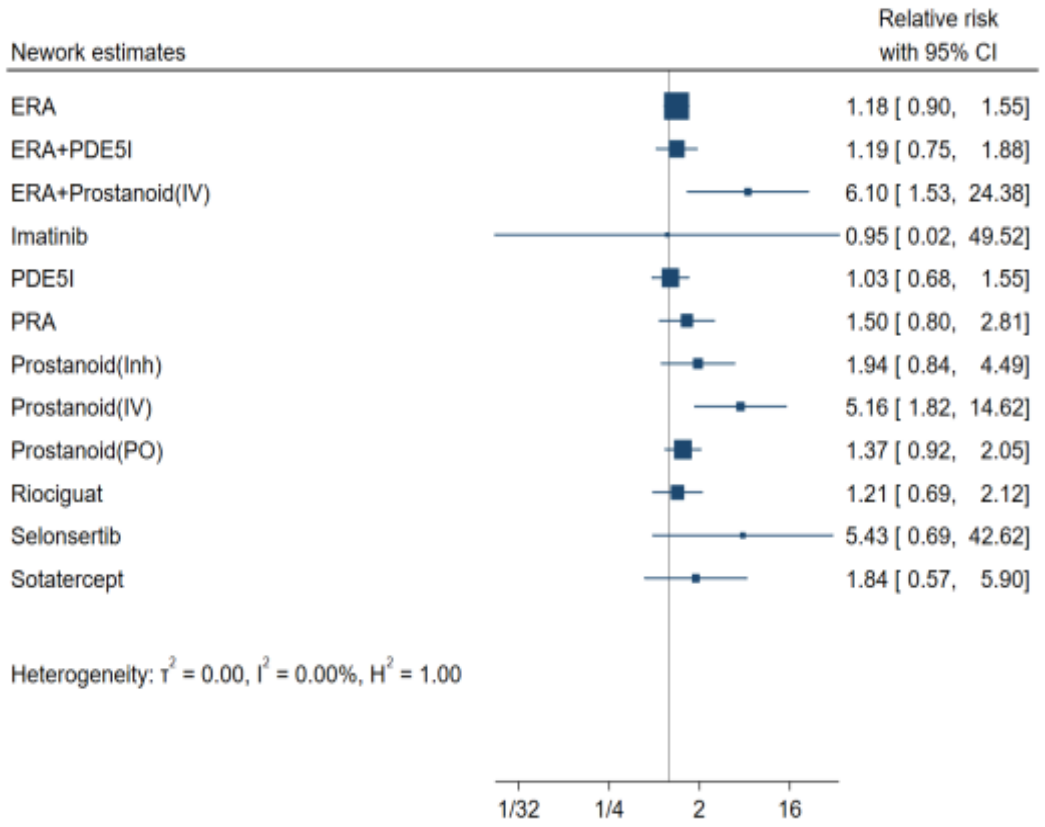
Contemporary Therapy is Not Making Our Patients Feel like They Are Living Well

Effect of Pulmonary Arterial Hypertension-Specific Therapies on Health-Related Quality of Life

A Systematic Review

es Lacasse, MD; Sylvie Martin, MSc; Sébastien Bonnet, PhD; and Steeve Provencher, MD

Functional class



BACKGROUND: Health-related quality of life (HRQoL) is severely impaired in pulmonary arterial hypertension (PAH). We aimed to assess the effect of PAH-specific therapies on HRQoL.

METHODS: A literature search was performed in MEDLINE and Embase databases (January 1990 to September 2013) to retrieve prospective placebo-controlled randomized trials of at least 6 weeks duration reporting the effect of PAH-specific therapies on HRQoL in adult patients with PAH. The articles were independently reviewed, and the validity of the trials was assessed using the Cochrane's Risk of Bias Tool.

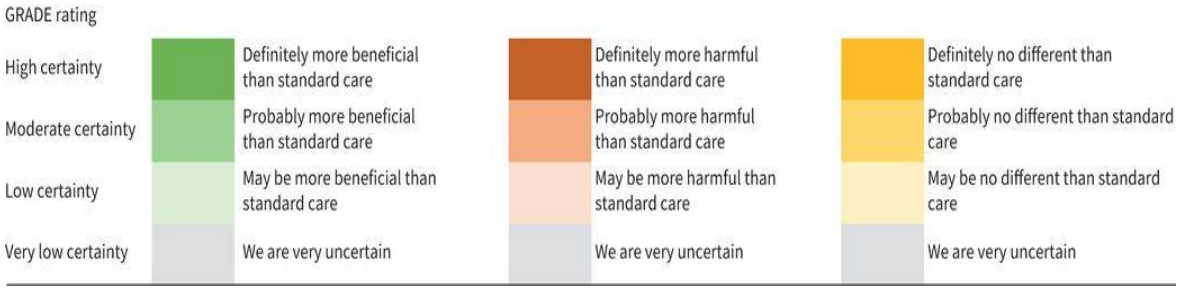
RESULTS: The literature search identified 1,172 titles. Seventeen articles reporting on 14 trials were retrieved, all of which were associated with a low risk of bias. The median study duration of the different trials was 12 weeks. Most patients had idiopathic PAH or PAH associated with connective tissue disease. A variety of HRQoL questionnaires were used in these trials, and most were generic. HRQoL results were most commonly minimally detailed, and some pivotal trials did not even assess HRQoL. Nevertheless, these trials consistently demonstrated statistically significant improvements in HRQoL with PAH-specific therapies, especially for the physical domains. In most cases, however, these improvements were smaller than the minimal important difference in HRQoL previously reported in PAH.

CONCLUSION: This review shows that PAH-specific therapies improve HRQoL in PAH. However, it remains difficult to draw any firm conclusion about the clinical significance of these improvements. Further work is mandatory to validate PAH-specific questionnaires that are responsive to clinical changes as well as to establish their interpretability.

CHEST 2014; 146(3):686-708

Rival G Chest, 146, (3), 2014, Pages 686-708

Medications for the Treatment of Pulmonary Arterial Hypertension: A Systematic Review and Network Meta-Analysis



Medication	Efficacy outcomes			Functional outcomes		Haemodynamic outcomes		Safety outcomes
	Clinical worsening	Mortality	Hospitalisation	Functional class	6MWD (m)	Cardiac output ($L \cdot min^{-1}$)	Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	SAE
ERA	−75.7 (−95 to −51.5)	−7.8 (−14.9 to 1.2)$^{\#}$	−29.3 (−43 to 11.1)$^{\#}$	23.8 (−12.6 to 71.5)$^{\#}$	31 (17.9 to 44.1)$^{\#}$	0.8 (0.1 to 1.5)$^{\#}$	0.55 (0.34 to 0.75)¶	−68.0 (−97.7 to −31.4)¶
ERA+PDE5i	−120.7 (−136.8 to −93.4)	−15.7 (−31.9 to 29)$^{+}$	−40.5 (−57 to −14)$^{\#}$	24.5 (−32.5 to 114.6)§	49.8 (25.9 to 73.8)$^{\#}$	1.6 (0.5 to 2.8)$^{\#}$		−80.1 (−138.9 to 18.7)$^{\#}$
Imatinib	29.1 (−47.4 to 167.4)$^{\#,f}$	0.41 (−25.3 to 66.4)$^{\#,f}$	20 (−35 to 139)^{f,§}	−6.3 (−127.6 to 6310)^{f,§}	29.8 (−3.5 to 63.1)$^{\#,f}$	0.7 (0.1 to 1.4)$^{\#,f}$		120.5 (−16.5 to 347.5)$^{\#,\S}$
PDE5i	−85.3 (−107.9 to −51.5)	−24.9 (−35.2 to 2.07)$^{\#}$ (direct)	−35.1 (−51.3 to 10.7)$^{\#}$	3.4 (−41.7 to 71.7)$^{\#}$	41.1 (24.9 to 57.1)$^{\#,\P}$	0.62 (0.1 to 1.14)$^{\#,f}$	0.44 (0.18 to 0.69)$^{\#}$	−74.9 (−119.9 to −10.6)$^{\#,f}$
PRA	−70.8 (−106.3 to −12.9)$^{\#}$	−2.1 (−10.8 to 8.7)$^{\#}$	−15.1 (−37.8 to 18.5)$^{\#}$	65 (−26 to 234)$^{\#}$	13.1 (10.8 to 15.39)$^{\#}$ (direct)		0.43 (0.07 to 0.78)$^{\#}$	−56.2 (−114.75 to 33.7)$^{\#}$
Prostanoid (inh)	−56 (−109.5 to 48.3)$^{\#}$	−28.2 (−38.5 to 20.3)§	−34.4 (−70 to 82.3)§	122.2 (−20.8 to 453.7)$^{\#}$	23.6 (0.9 to 46.2)$^{\#}$	0.5 (0.01 to 0.98)$^{\#,\P}$	0.38 (−0.09 to 0.86)$^{\#,f}$	11.25 (−81 to 159.7)§

Medication	Efficacy outcomes			Functional outcomes		Haemodynamic outcomes		Safety outcomes
	Clinical worsening	Mortality	Hospitalisation	Functional class	6MWD (m)	Cardiac output ($L \cdot min^{-1}$)	Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	SAE
Prostanoid (inh)+ERA	−112.7 (−148.1 to 20.9)$^{\#,f}$	−4.1 (40.6 to 1756.2)$^{+}$			115 (78.8 to 151.1)$^{\#,f}$		1.02 (0.54 to 1.51)	−66.7 (−219.3 to 4161)$^{\#,\S}$
Prostanoid (*i.v./s.c.*)	−85.3 (−119.1 to −24.1)$^{\#}$	−18.26 (−28.6 to 0)$^{\#}$		540.8 (106.6 to 1771)$^{\#}$	55.1 (33 to 77.3)$^{\#,\P}$	0 (−0.98 to 0.98)^{f,§}	0.35 (0.12 to 0.59)$^{\#}$	−42.7 (−110.2 to 58.5)§
Prostanoid (*i.v./s.c.*) +ERA		12.4 (−39.01 to 1048.3)$^{+}$		662.8 (68.3 to 3039.5)$^{\#,f}$	61.1 (1.65 to 120.6)^{f,§}	1.50 (0.69 to 2.29)^{f}	0.55 (−0.08 to 1.19)$^{\#}$	−101.1 (−203.5 to 488.61)§
Prostanoid (oral)	−38.6 (−77.3 to 17.7)$^{\#}$	−5.8 (−17 to 11.6)§	−4.2 (−31.9 to 42)§	65 (−26 to 234)$^{\#,f}$	19.6 (0.6 to 38.6)$^{\#}$		0.12 (−0.23 to 0.49)$^{\#}$	−13.5 (−78.7 to 78.7)§
Riociguat	−133.6 (−151.3 to −85.3)	−29 (−38.6 to 8.7)$^{\#}$	−77.3 (−82.5 to −52.9)	27.3 (−40.3 to 145.6)§	49.5 (17.3 to 81.7)$^{\#}$	1.01 (0.33 to 1.68)$^{\#}$		−135 (−175.5 to 56.2)§

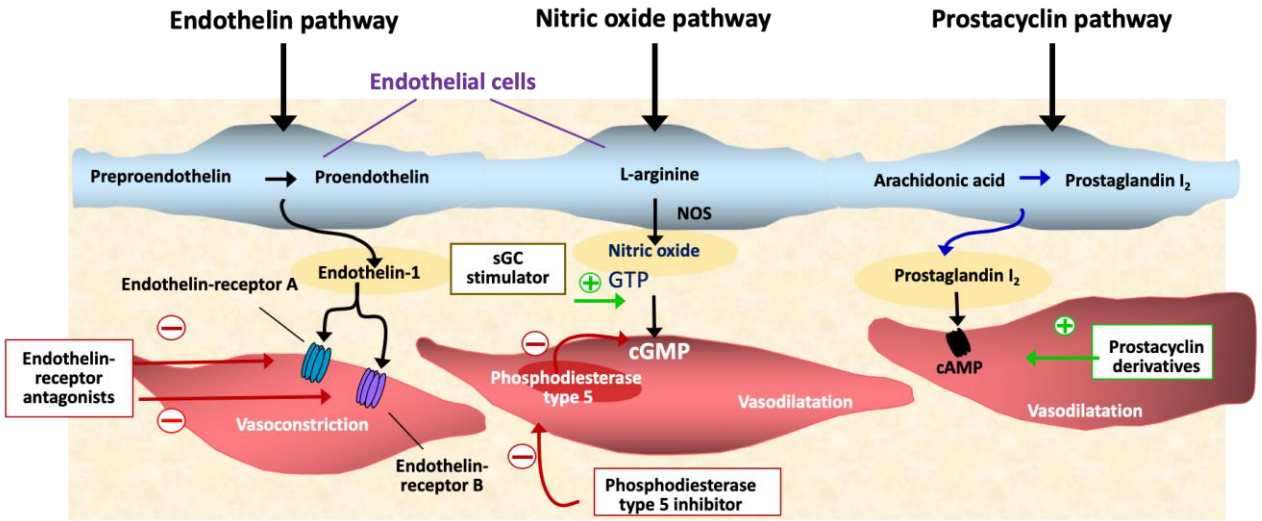
Pitre, T European Respiratory Review 2022 31: 220036; DOI: 10.1183/16000617.0036-2022

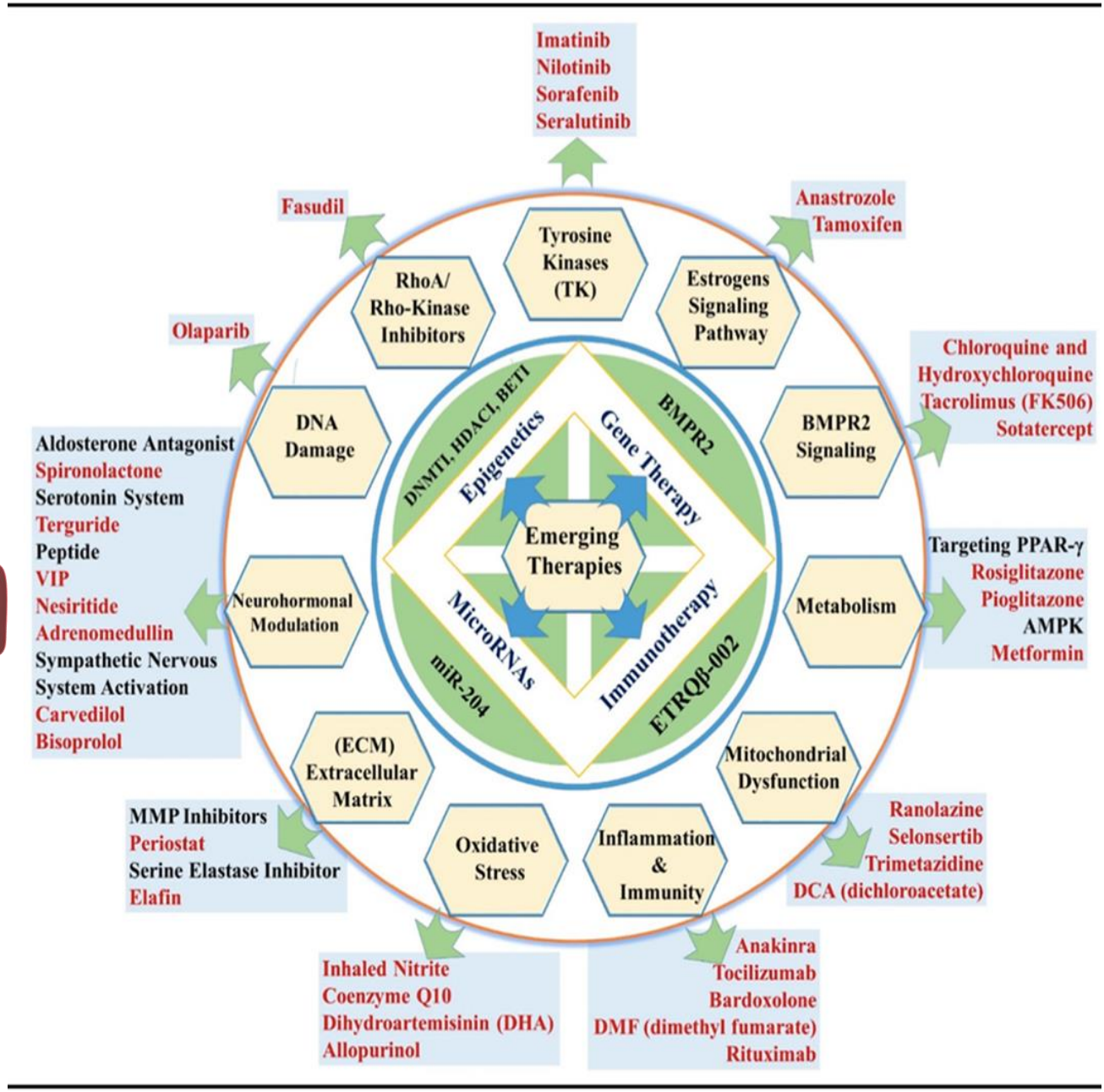
What do our Current Drugs Do?

Do they change the Pathology of the Disease

Icahn
School of
Medicine at
Mount
Sinai

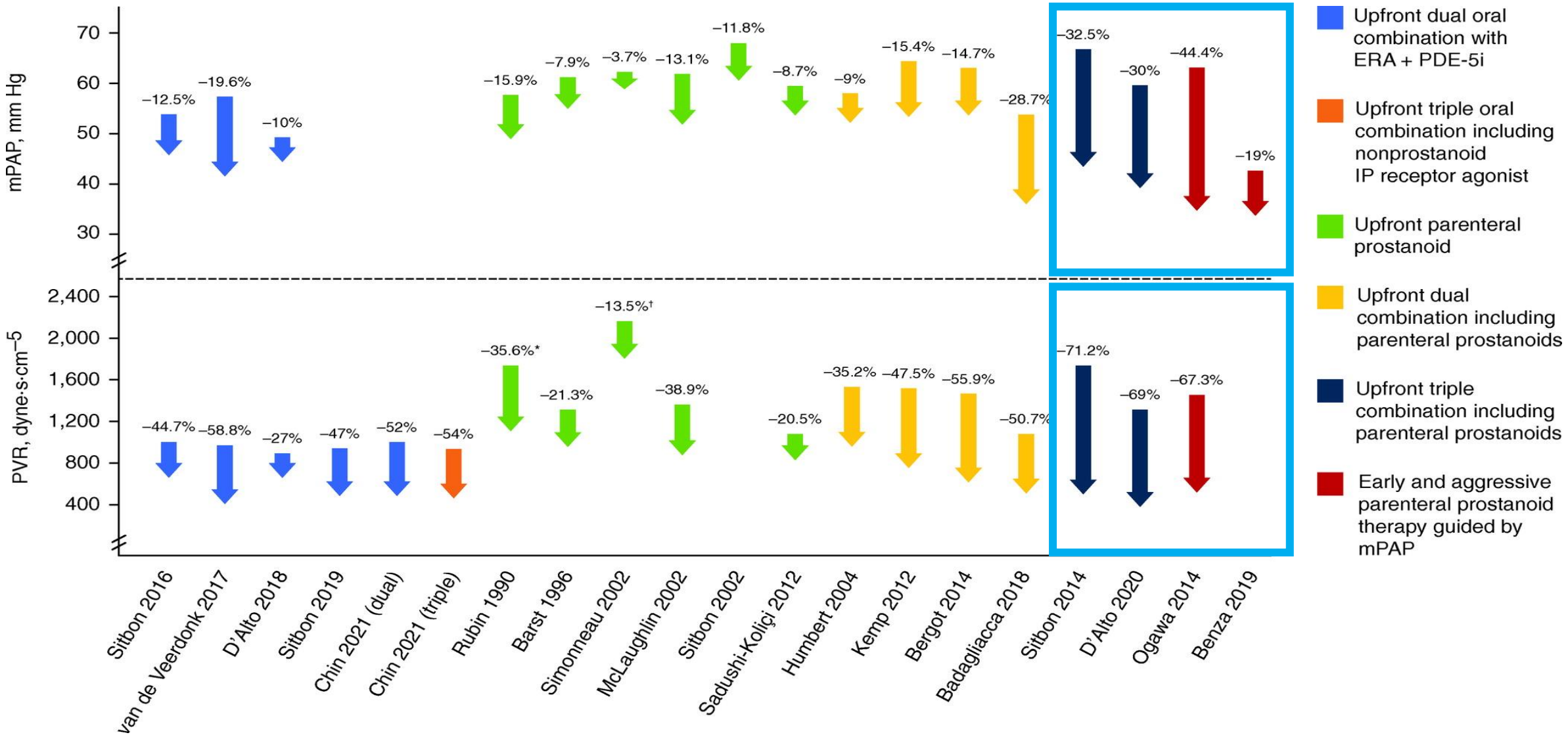
Expanded Knowledge of Pathophysiology: Why Should We Sit on What We Know?





Shah AJ, *International Journal of Molecular Sciences*. 2023; 24(6):5850.

Are We Really Remodeling the Pulmonary Vascular Bed with Current Therapeutics



Vizza CD, Am J Respir Crit Care Med, 2022

Current Drugs are Not Tissue Targeted

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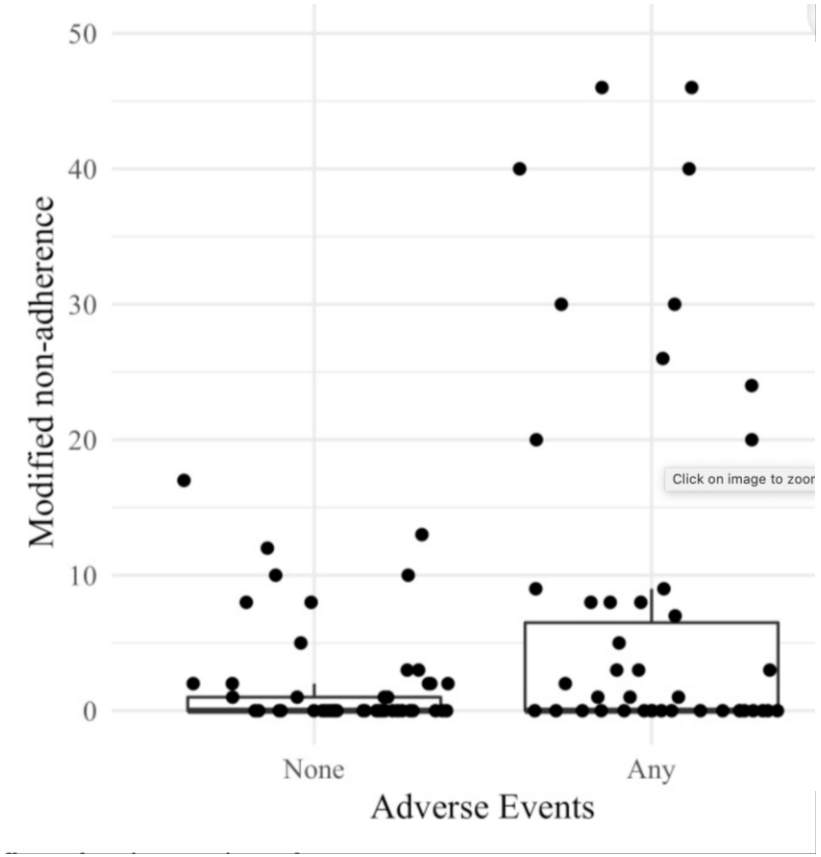
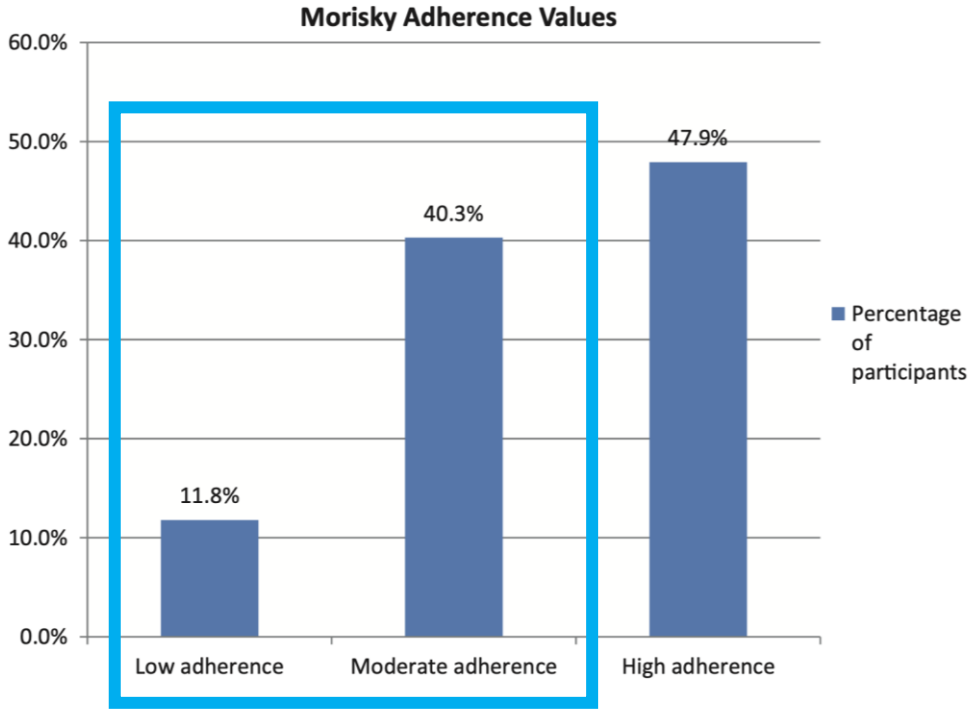
Terrible Side Effects with Our Contemporary Medications That is Compounded by Multiple Drug Use

FDA-Approved Medications in the Treatment of PAH

Drug (Brand)	Adverse Effects
Epoprostenol (Flolan)	Central line infections, flushing, n/v, hypotension, headache, flulike symptoms, jaw pain
Treprostinil (Remodulin)	Headache, n/v, infusion site reactions and pain, flulike symptoms, jaw pain
Treprostinil (Tyvaso)	Headache, flushing, nausea, cough, throat irritation
Iloprost (Ventavis)	Flushing, hypotension, headache, flulike symptoms, trismus, cough
Bosentan (Tracleer)	Respiratory tract infections, peripheral edema, headache, anemia, chest pain, syncope; black box warnings for hepatotoxicity and teratogenicity
Ambrisentan (Letairis)	Peripheral edema, headache, nasal congestion, flushing; black box warnings for potential hepatotoxicity and contraindication in pregnancy
Sildenafil (Revatio)	Epistaxis, headache, dyspnea, flushing, NAION, hearing loss
Tadalafil (Adcirca)	Headache, myalgias, nasopharyngitis, flushing, respiratory tract infections, hypotension, hearing or vision loss

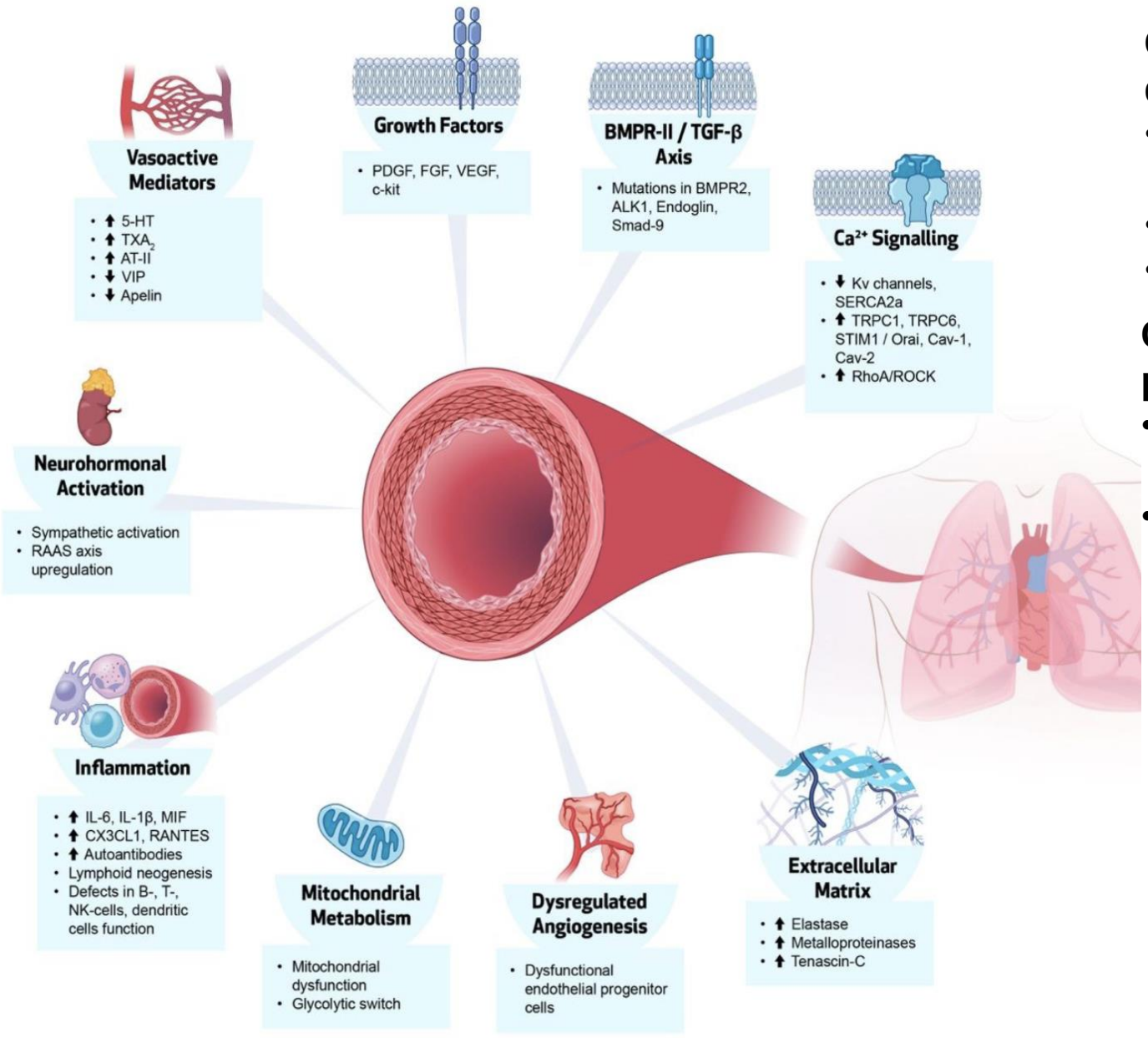
47% of of PAH patients Experience Significant AE From Their Medication





Shah NB, PLoS One. 2019 Jun 6;14(6):e0217798. Grady, D Pulmonary circulation 8, no. 1 (2017): 2045893217743616.

Multifactorial pathogenesis and Potential Targets for Therapeutic Interventions in PAH



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**

Sahay S Am J Respir Crit Care Med. 2024 Jul 10.. Woodcock ; J Cardiovasc Pharmacol Ther. 2019 Jul; 24(4): 334–354.

New Pathway Development: Failed or Neutral Clinical Trials

Main recent clinical trials in pulmonary arterial hypertension with either negative result or tolerability/safety issues

Study/compound(s)	Phase	End-point: result	Formal presentation [ref.]	Published [ref.]
ASA-STAT: aspirin and simvastatin	2	6MWD: lack of efficacy	Yes	Yes [103]
ARROW: selonsertib (ASK-1 inhibitor)	2	6MWD: lack of efficacy	Yes [62]	No
Cicletanine (antihypertensive with vasorelaxant and diuretic properties)	2	PVR: lack of efficacy	Yes [104]	No
Aviptadil (vasoactive intestinal peptide)	2	PVR: lack of efficacy	Yes [105]	No
IMPRES: imatinib (tyrosine kinase inhibitor)	3	6MWD: positive tolerability and safety issues	Yes	Yes [45]
Terguride (partial dopamine agonist and serotonin receptor antagonist)	2	6MWD: lack of efficacy	Yes [68]	No
LIBERTY: ubenimex (leukotriene B4 inhibitor)	2	PVR: lack of efficacy	No	No

6MWD: 6-min walk distance; ASK1: apoptosis signal-regulating kinase 1; PVR: pulmonary vascular resistance.

Manipulating PDGF

Iminitab: AV-101-002 Study: Aerovate Therapeutics; Trials of AV-101, an inhaled, dry powder aerosol version of Novartis' cancer drug Gleevec (imatinib)

Manipulating Serotonin:

ELEVATE-2 Study: Altavant Sciences; rodatristat ethyl ("rodatristat") orally bioavailable, direct and reversible tryptophan hydroxylase (TPH) inhibitor designed to block peripheral serotonin production

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

Conclusions

With Contemporary Therapy:

- Mortality has improved, but remains suboptimal
- Morbidity remains substantial
- Suboptimal improvements in patient well being and functional capacity
- Traditional pathways now only a small subset of available pathways to develop effective downstream therapeutics
- Side effects are prominent leading to suboptimal drug compliance
- Tissue Targeting is limited; new enabling targeting paradigms are within reach

Role of CS1

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

A Phase 2, **P**rospective, **R**andomized, **O**pen-label, **B**linded **E**ndpoint, Multicenter Study to Investigate Safety and Tolerability, PK and Exploratory Efficacy of 3 Doses of CS1 in Subjects with Pulmonary Arterial Hypertension

Phase 2a Study of CS1 in Subjects with Pulmonary Arterial Hypertension

1. **Novel Compound with Novel Action**
2. **Novel and Innovative Endpoints**

   REVEAL Risk Score

   Cardiac MRI

   CardioMEMs device

   Novel biomarkers

3. **Traditional Endpoints (efficacy and safety)**

   6MWD,
   Hemodynamics,
   Echo,
   Biomarkers (NT PROBNP)

Agenda

Time	Discussion Item	Speaker
13:30	**Welcome**	
13:35	**Introduction to Cereno Scientific**	**Sten R. Sörensen** *CEO, Cereno Scientific*
13:50	**Understanding PAH, a debilitating rare disease**	**Dr. Raymond Benza** *Network Director of Pulmonary Hypertension at Mount Sinai Icahn School of Medicine, New York City*
14:10	**Cereno Scientific's CS1 in PAH**	**Dr. Rahul Agrawal,** *CMO and Head of R&D, Cereno Scientific*
14:15	**Cereno Scientific's CS1 - Phase IIa trial results**	**Dr. Rahul Agrawal,** *CMO and Head of R&D, Cereno Scientific* **Nicholas Oakes,** *Head of Preclinical Development, Cereno Scientific*
14:40	**Investigator and patient perspective of CS1-003 trial**	**Dr. Jason Guichard** *Cardiologist at Prisma Health-Upstate, Assistant Professor of Medicine, University of South Carolina School of Medicine Greenville and investigator in the Phase IIa trial of CS1 in PAH*

Dr. Rahul Agrawal
CMO and Head of R&D

Cereno Scientific's CS1 in PAH

Cereno Scientific

Cereno's portfolio is uniquely positioned to make impact in diseases with high unmet medical needs

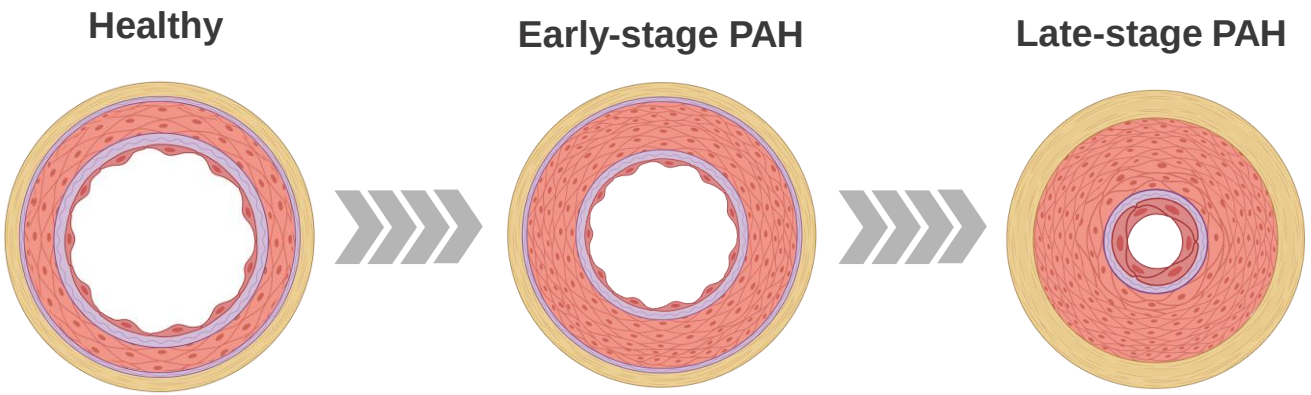
Program	Target	Indication	Preclinical	Phase I	Phase II	Phase III	Status
CS1	HDACi with disease-modifying potential	PAH					Phase II top-line results in Q3 2024[1] Expanded Access Program initiated in Q1 2024[1]
CS014	HDACi with disease-modifying potential	IPF					Phase I initiated in Q2 2024[2]
CS585	PRA oral, selective and potent	CVD					Ongoing preclinical development during 2024/25

Note: Progress bars are only an estimation, not to scale.

Source: 1. Cereno Press Release, 21st Feb 2024; 2. Cereno Press Release, 18th June 2024

Epigenetic mechanism through HDAC drives PAH progression

Pathological remodeling of small pulmonary arteries



PAH pathophysiology

- Endothelial dysfunction
- Inflammation
- Fibrosis
- Plexiform lesions
- Vasoconstriction
- Vascular & RV hypertrophy

Clinical consequence → Risk score and functional class deterioration

HDAC: Histone deacetylase. RV: Right ventricular.

Existing treatment options are insufficient in PAH

Current therapies do not address the root cause of the disease

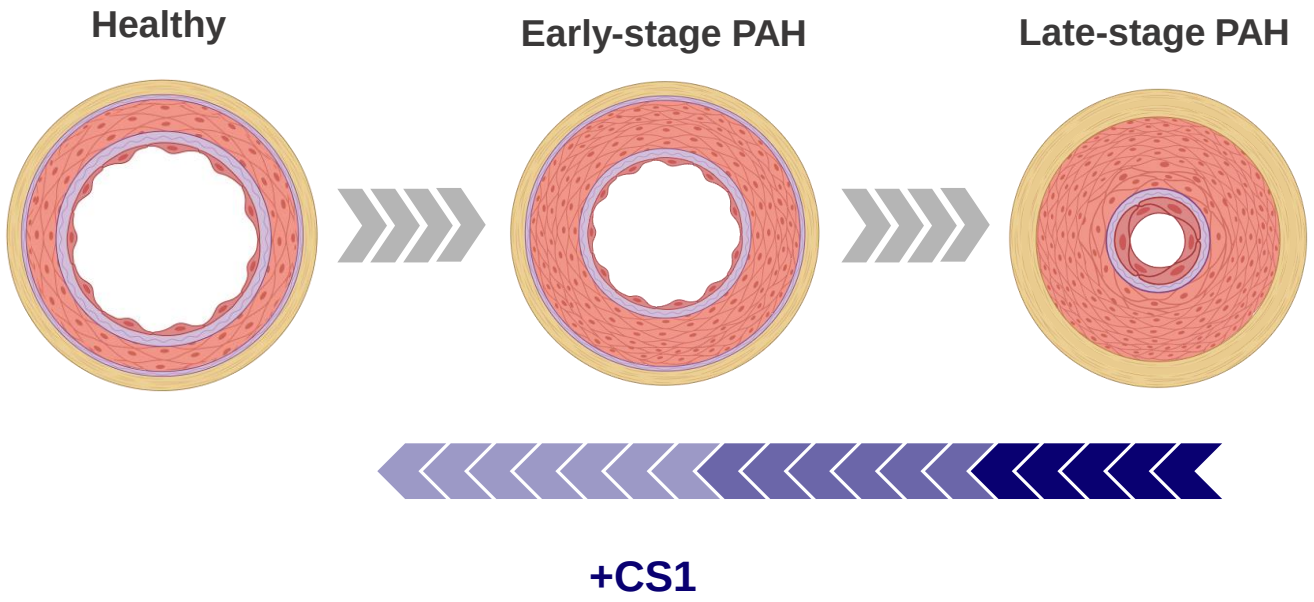
Key unmet needs in PAH:

- Therapies that have disease-modifying capacity
- Safer and more tolerable treatments

CS1 aims to address the unmet medical needs

CS1 tackles PAH root cause through reverse remodeling

CS1 is developed as a disease-modifying therapy



CS1 characteristics in preclinical models

- Reverse pathological remodeling
- Anti-fibrotic
- Anti-inflammatory
- Pulmonary pressure reduction
- Anti-thrombotic (fibrinolytic, anti-platelet)

Objective of reverse remodeling → Risk score and functional class improvement

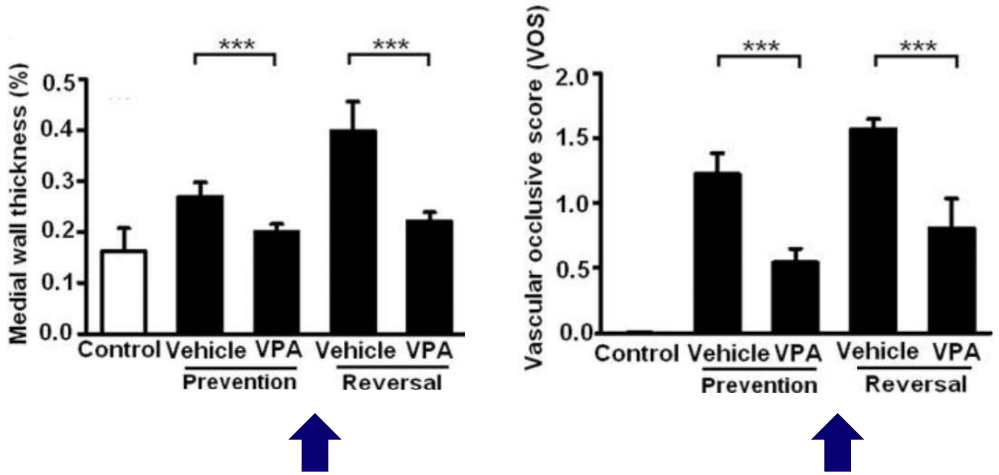
PAH preclinical data – Prevention and reversal of pathological remodeling and reduced mPAP

RESEARCH ARTICLE

Therapeutic Efficacy of Valproic Acid in a Combined Monocrotaline and Chronic Hypoxia Rat Model of Severe Pulmonary Hypertension

Beidi Lan, Emiko Hayama, Nanako Kawaguchi, Yoshiyuki Furutani, Toshio Nakanishi*

Department of Pediatric Cardiology, Tokyo Women's Medical University, Tokyo, Japan

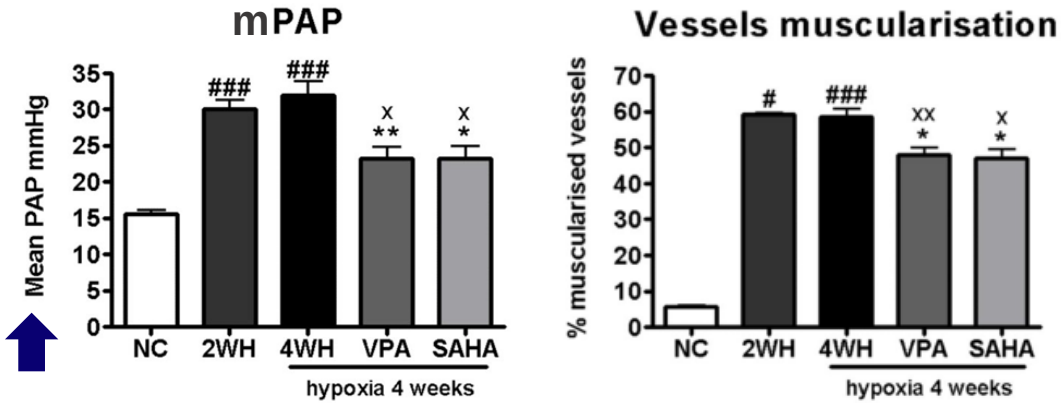


Histone deacetylation inhibition in pulmonary hypertension: therapeutic potential of valproic acid (VPA) and suberoylanilide hydroxamic acid (SAHA)

Lan Zhao, M.D PhD[1,*], Chien-Nien Chen, M.D[1], Nabil Hajji, PhD[1], Eduardo Oliver, PhD[1], Emanuele Cotroneo, PhD[1], John Wharton, PhD[1], Daren Wang, PhD[2], Min Li, PhD[2], Timothy A. McKinsey, PhD[2], Kurt R. Stenmark, M.D[2], and **Martin R. Wilkins, M.D[1]**

[1]Centre for Pharmacology and Therapeutics, Experimental Medicine, Imperial College London, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK

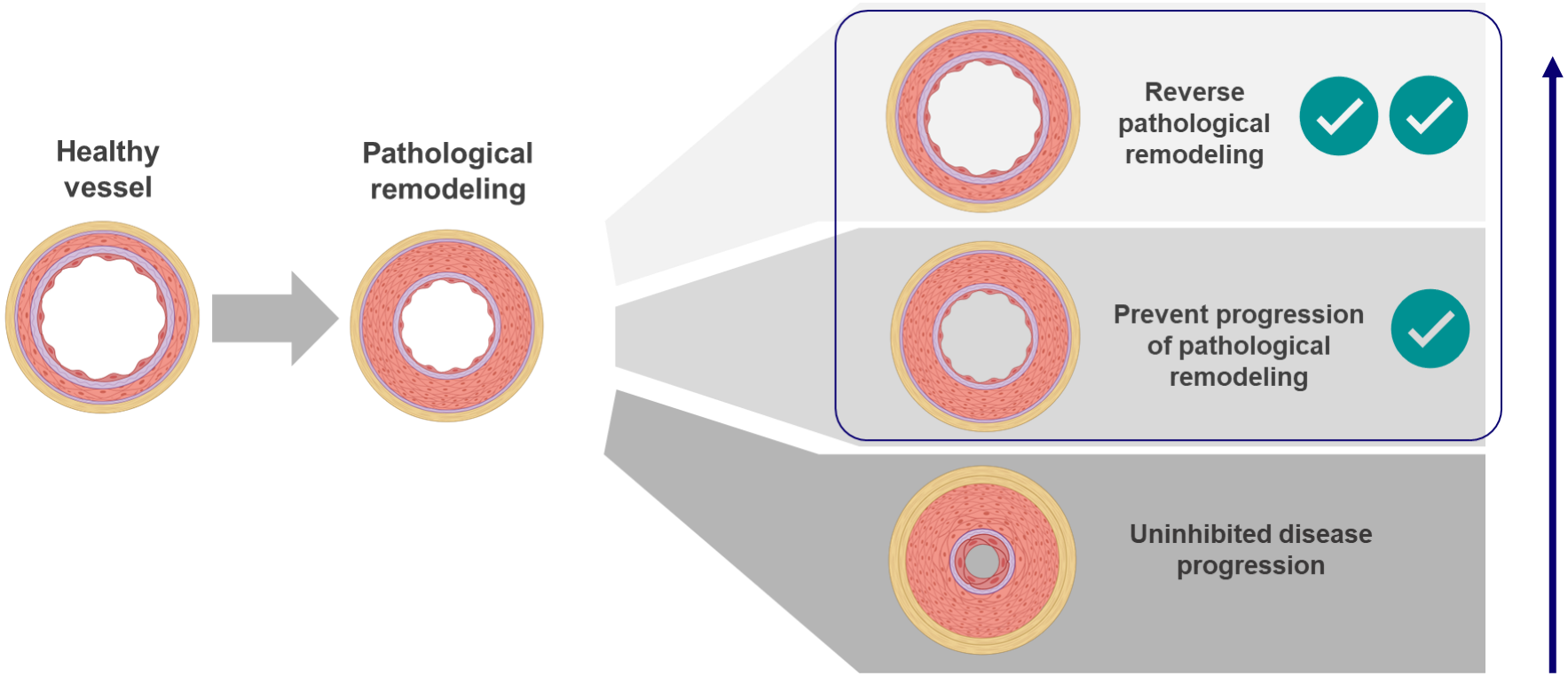
[2]Department of Pediatrics, Division of Critical Care Medicine, University of Colorado Denver, USA



PAP: Pulmonary artery pressure.

Source: Lan et al PLoS ONE, 2015; Zhao, L. et al., Circulation, 2012.

Goal of PAH therapy – Prevent and reverse pathological remodeling



Clinical goal of therapy:

- **Improvement of risk score**
- **Improvement of functional class**

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Dr. Rahul Agrawal
CMO and Head of R&D

Dr. Nicholas Oakes
Head of Preclinical Development

CS1-003 Phase IIa study results

Cereno Scientific

CS1-003: A phase IIa, prospective, randomized, multicenter trial to investigate the safety, tolerability and explore efficacy of CS1 in Pulmonary Arterial Hypertension (PAH)

NCT05224531

Cereno Scientific

CS1 PAH phase IIa trial – Summary results

- **Primary endpoint of safety & tolerability met successfully**
- Positive impact on exploratory clinical efficacy parameters:
  - **REVEAL risk score**: 43% improved; 71% improved or stable
  - **Functional class**: 33% improved; 86% improved or stable
  - **mPAP**: 67% had sustained pressure reduction
- CS1 study data, together with preclinical information, is **consistent with reversing pathological remodeling**

➡ Clear path forward - Engaging with regulatory authorities for pivotal trial

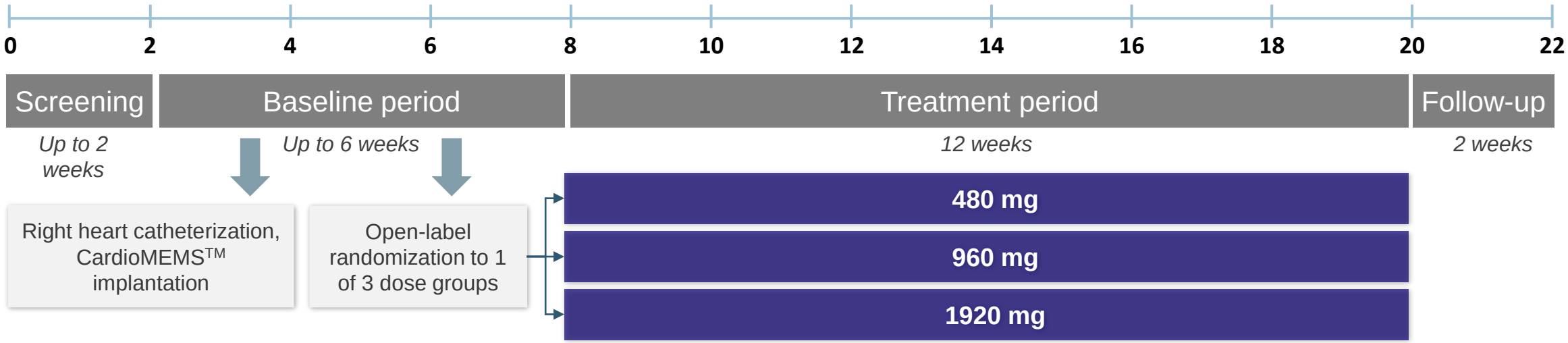
CS1 PAH phase IIa trial design

Primary endpoint: **Safety and tolerability**

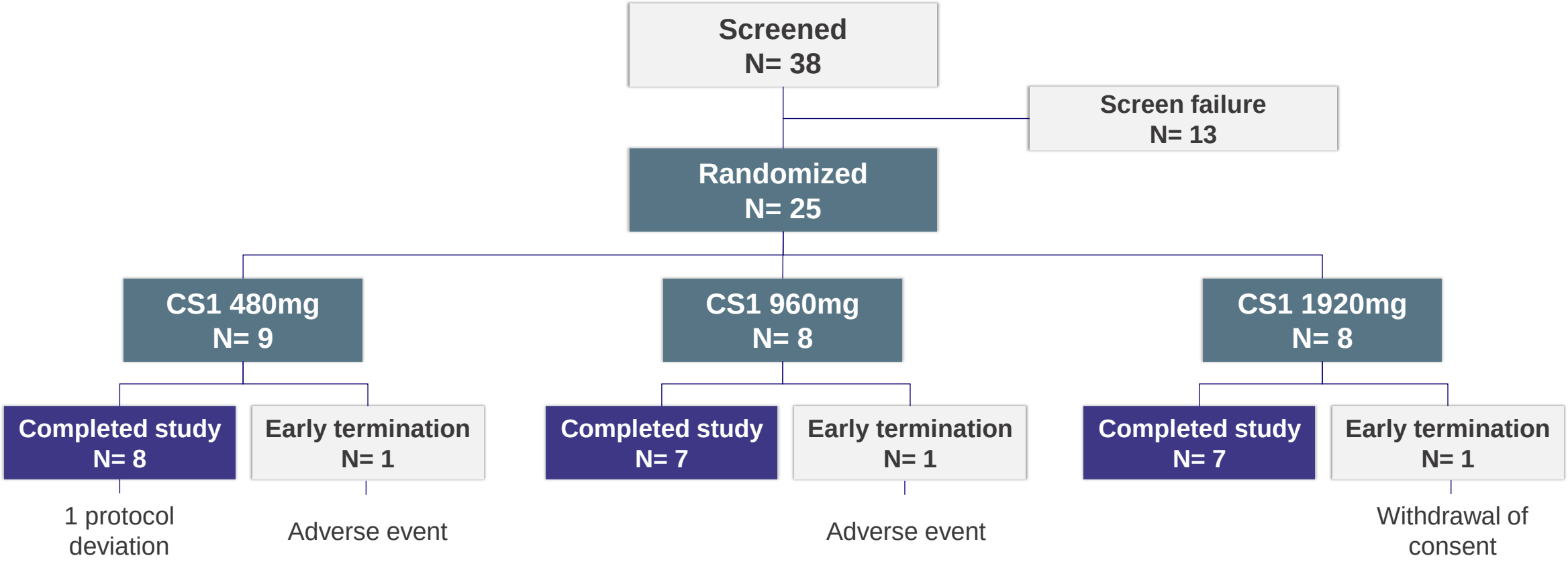
Exploratory endpoints: Including validated risk score, functional class

Implanted device for pulmonary pressures

Trial size: 25 patients 10 US clinical sites



CS1 Phase IIa trial – 25 patients randomized for safety analysis, 21 patients per protocol



Per protocol: 21 patients who completed the treatment without protocol deviation

CS1 Phase IIa trial – Demographic and clinical characteristics at baseline show representative PAH population

Variable	Overall (N=25)
Female Sex	19 (76.0%)
Race	
White	16 (64.0%)
Black or african American	4 (16.0%)
Asian	1 (4.0%)
Native american or alaska native	1 (4.0%)
Other	3 (12.0%)
NICE Clinical Classification of PAH category	
Idiopathic PAH	20 (80.0%)
Heritable PAH	1 (4.0%)
Drug or toxin-induced	3 (12.0%)
PAH associated with connective tissue disease	1 (4.0%)
NYHA/WHO Functional Class Assessment	
Class II	10 (40.0%)
Class III	15 (60.0%)
Pulmonary vascular resistance (Wood unit)	8.0±2.3
Mean Pulmonary Arterial Pressure (mmHg)	47.8±9.2

CS1 – Phase IIa safety data

- Primary endpoint successfully met
- Good safety and tolerability profile

Primary Endpoint met – No serious adverse events related to CS1

Treatment-Emergent Adverse Events (TEAEs)	CS1 480 mg QD (N=9)	CS1 960 mg QD (N=8)	CS1 1920 mg QD (N=8)	Overall (N=25)
	Subjects n (%)	**Subjects n (%)**	**Subjects n (%)**	**Subjects n (%)**
Any TEAEs	6 (66.7%)	5 (62.5%)	8 (100.0%)	19 (76.0%)
Serious TEAEs	2 (22.2%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
Treatment-related TEAEs	2 (22.2%)	3 (37.5%)	6 (75.0%)	11 (44.0%)
Serious Treatment-related TEAEs	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
TEAE Leading to Study Drug Discontinuation	1 (11.1%)	1 (12.5%)	0 (0.0%)	2 (8.0%)
TEAE leading to dose reduction	0 (0.0%)	2 (25.0%)	2 (25.0%)	4 (16.0%)

Primary endpoint of safety & tolerability successfully met

CS1 showed good safety & tolerability profile

Safety

- No CS1-related serious adverse events including hospitalizations/mortality
- No CS1-related changes in liver lab values
- No CS1-related clinically significant platelets decrease or bleedings

Tolerability

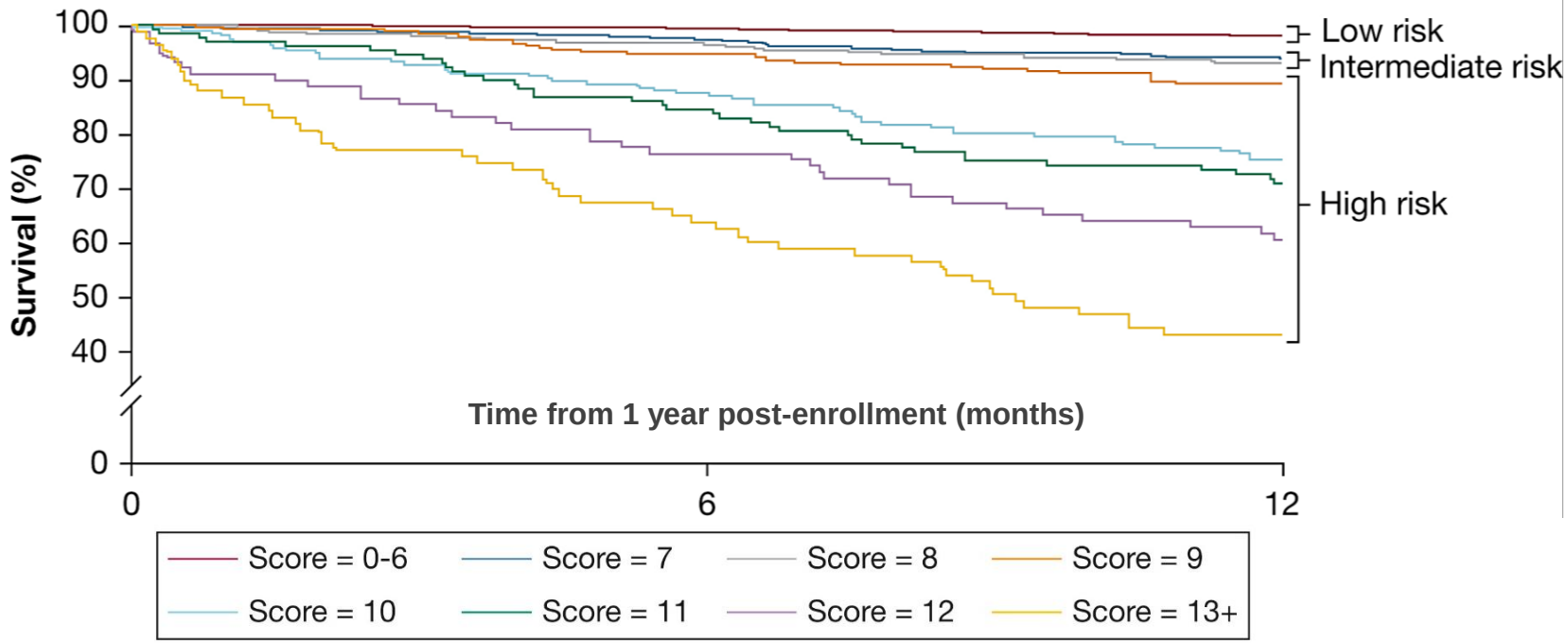
- CS1 was well tolerated

CS1 phase IIa – Compelling positive signs of efficacy

- Reduction in REVEAL risk score
- Improvement in functional class
- Reduction in mean pulmonary arterial pressure (mPAP, AUC)

REVEAL risk score predicts survival

Published data: REVEAL score has the highest prognostic power



Published data (Benza et al., 2022):

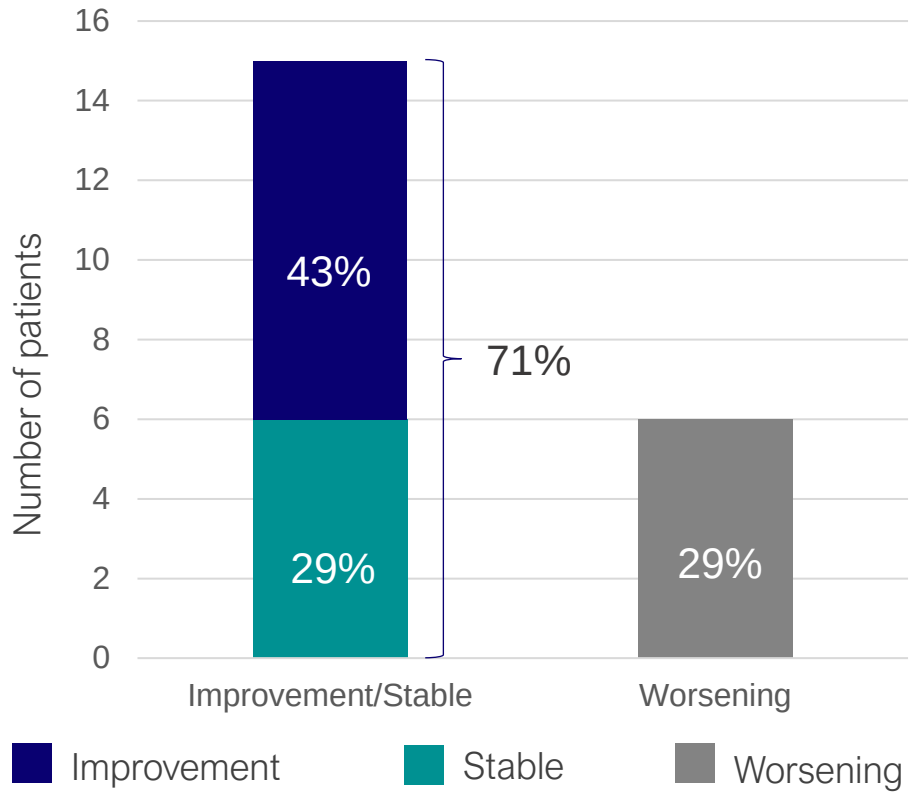
1-point reduction in risk score in 12 weeks associated with 23% reduction in relative risk of death at 12 months[1]

REVEAL risk score parameters: WHO subgroup, demographics & comorbidities, functional class, vital signs, 6MWT, BNP/NT-proBNP, echocardiogram, pulmonary function test, right heart catheterization.

Benza R., et al Chest 2019; Benza RL et al J Heart Lung Transplant 2022

CS1 phase IIa – Compelling signs of efficacy (1)
REVEAL risk score: 43% of the patients improved

REVEAL risk score change from baseline



- **43%** of the patients (9/21) improved by at least 1 point **reduction** in REVEAL risk score
- **71%** of the patients (15/21) **improved** or had **stable** REVEAL risk score

Published data (Benza et al., 2022):

1-point reduction in risk score in 12 weeks associated with 23% reduction in relative risk of death at 12 months[1]

Improvement: At least 1 point reduction in REVEAL risk score. Worsening: At least 1 point increase in risk score.

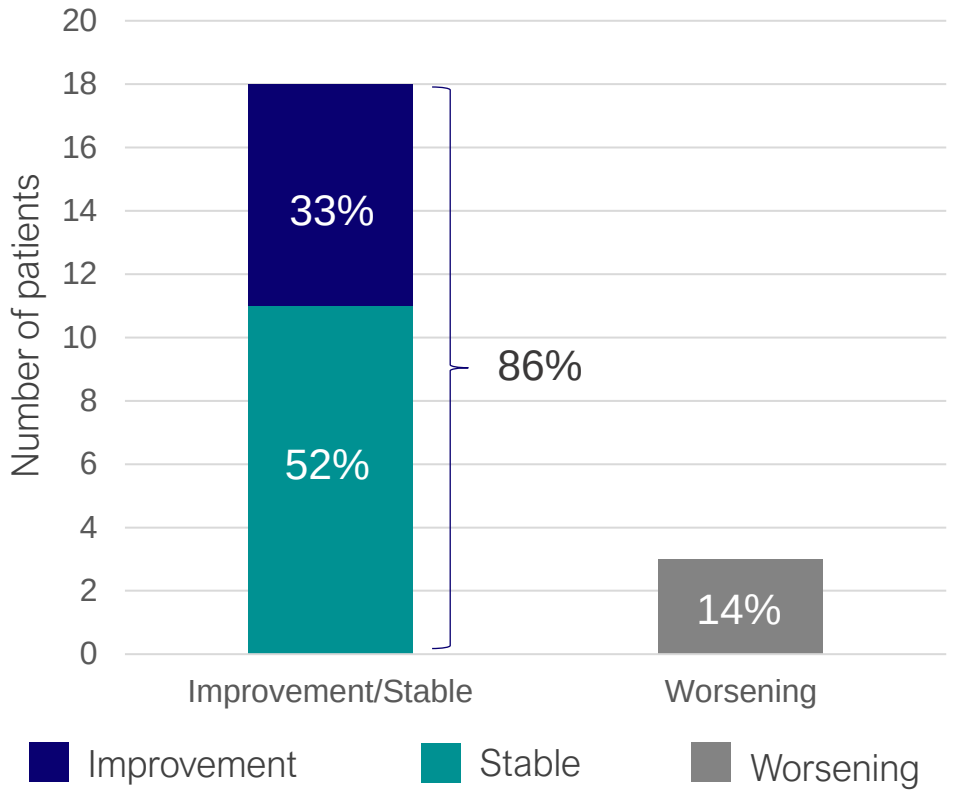
Cereno Scientific

Percentages are rounded; as a result, the sum of the individual numbers does not always add up to 100%.

1. Benza RL et al J Heart Lung Transplant 2022

CS1 phase IIa – Compelling signs of efficacy (2)
Functional Class: 86% improved or had stable functional class

NYHA Functional Class change from baseline



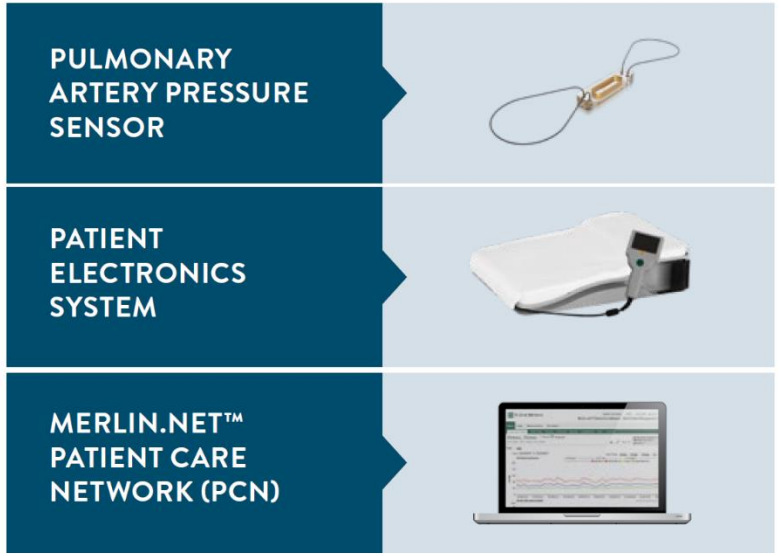
- **33%** (7/21) of patients **improved** functional class
- **86%** (18/21) **improved** or had **stable** functional class

Functional class: Describes how severe a patient's symptoms and limitations are

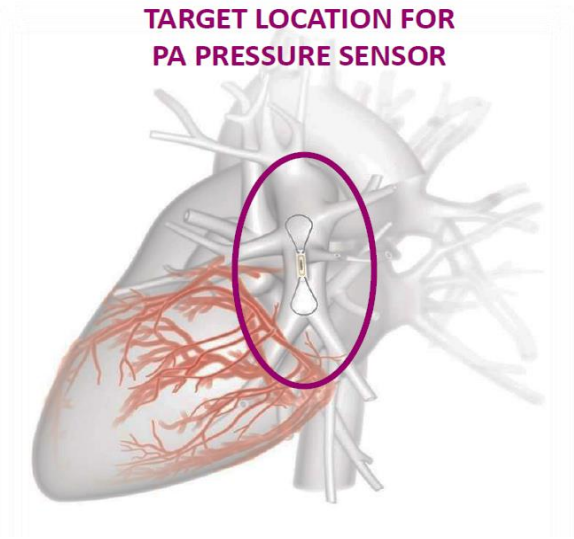
Cereno Scientific

Percentages are rounded; as a result, the sum of the individual numbers does not always add up to 100%.

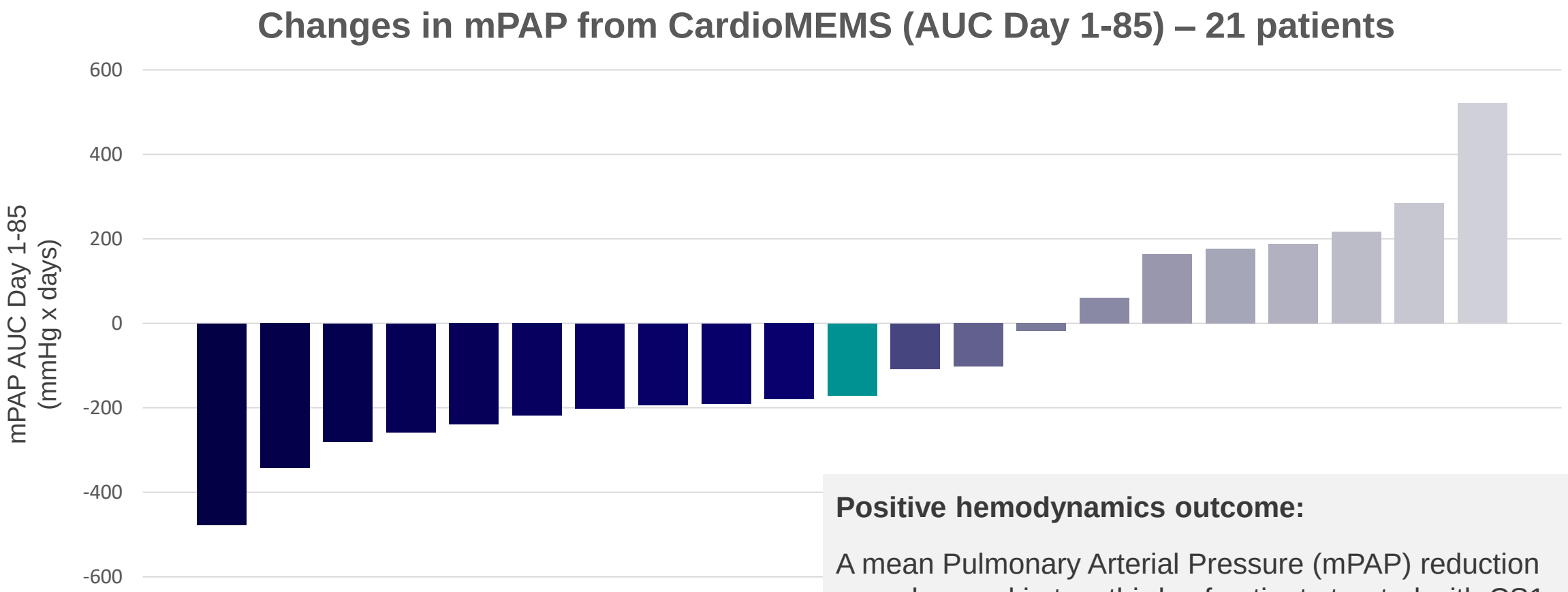
CS1 phase IIa trial – CardioMEMS permits daily non-invasive monitoring of pulmonary arterial pressure



Mean Pulmonary Arterial Pressure (mPAP) area under the curve (AUC) is a measure of the pressure burden of pulmonary pressure on the right ventricle of the heart



CS1 phase IIa trial – Compelling signs of efficacy (3)
CardioMEMS: Sustained reduction of mPAP AUC in 67% (14/21) of patients

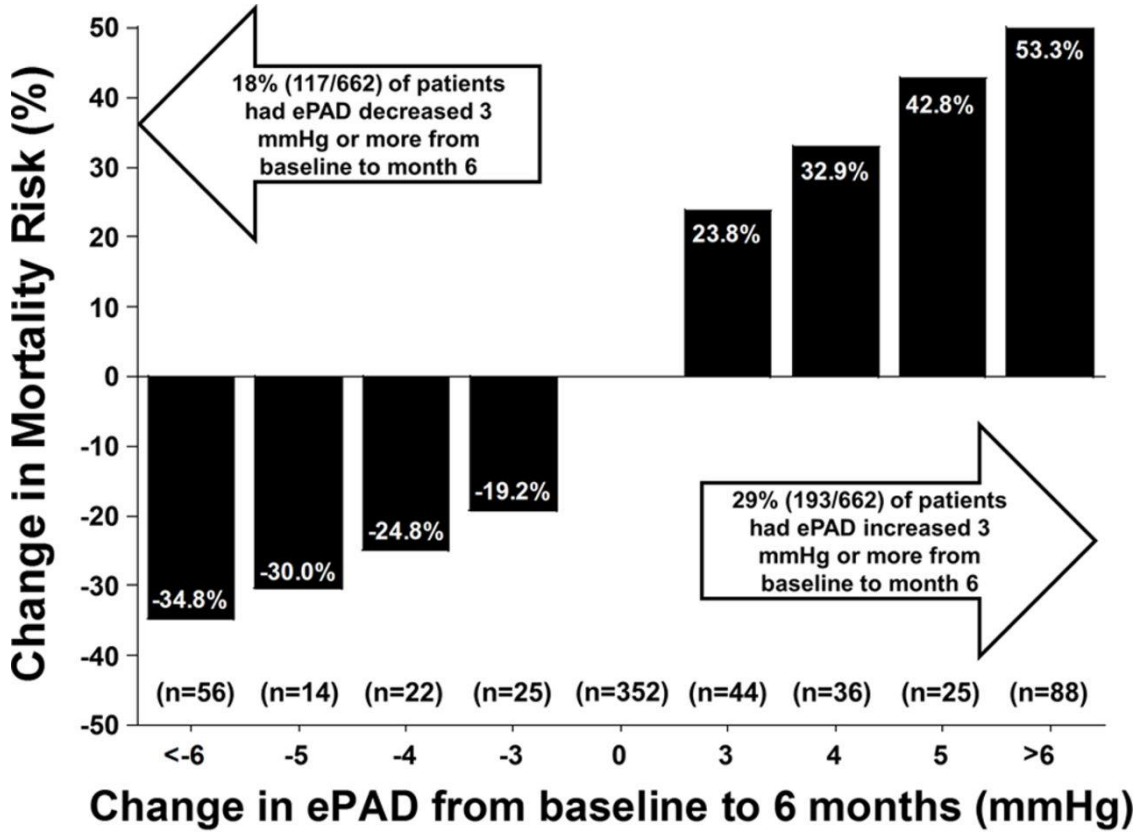


Positive hemodynamics outcome:

A mean Pulmonary Arterial Pressure (mPAP) reduction was observed in two-thirds of patients treated with CS1.

Even a small change (3-5mmHg) in pulmonary artery diastolic pressure (ePAD) is an independent predictor of mortality

Relationship between change in ePAD and mortality



Published data:

Decreased ePAD of 3, 4, or 5 mmHg from baseline to 6 months was **associated with decreased mortality risk**

Source: Zile MR, Bennett TD, El Hajj S, et al. Circ Heart Fail. 2017

CS1 PAH phase IIa trial – Summary of results

- **Primary endpoint of safety & tolerability met successfully**
- **Compelling positive impact** on exploratory clinical parameters **already over 12-week treatment**:
  - **REVEAL risk score:**
    - **43%** (9/21) of the patients **improved** risk score
    - **71%** (15/21) of the patients **improved** or had **stable** risk score
  - **Functional Class:**
    - **33%** (7/21) of the patients **improved** functional class
    - **86%** (18/21) of the patients **improved** or had **stable** functional class
  - **Mean pulmonary arterial pressure (mPAP, AUC):**
    - **67%** (14/21) of the patients had **sustained pressure reduction**

In-depth analysis

- Recent inhouse evidence of reverse remodeling from preclinical data
- Pulmonary Vascular Resistance (PVR) in the CS1 Phase IIa trial
- Remarkable responders: evidence consistent with reverse remodeling and improved RV function in the CS1 Phase IIa trial
- Overall findings suggest lower dose range optimal

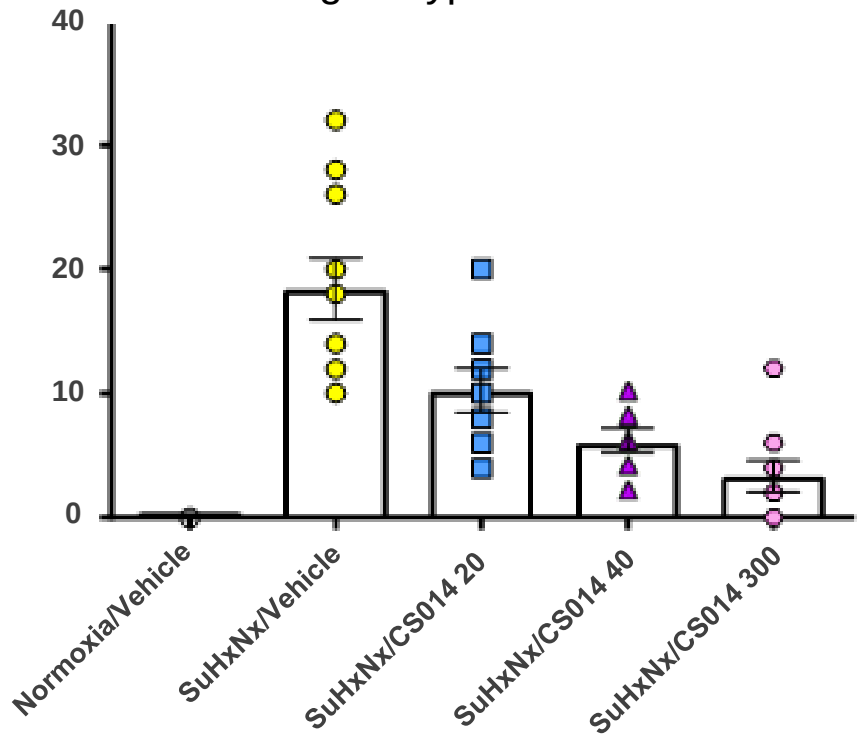
Nicholas Oakes
Head of Preclinical Development

Preclinical data – Dose-dependent reduction of plexiform lesions

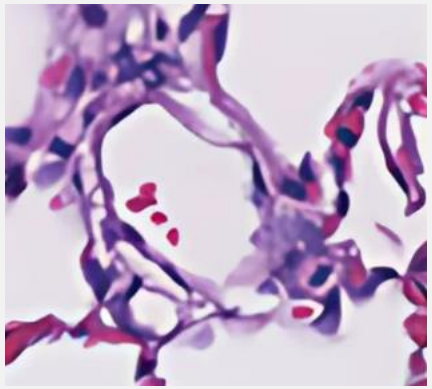
Hallmark of PAH vascular remodeling

Reduced incidence of plexiform lesions in small pulmonary arteries (<100µm) (%)

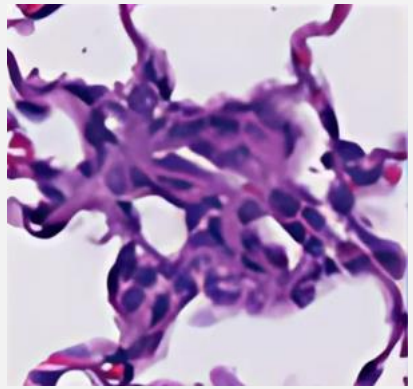
Sugen/hypoxia rat model



Healthy



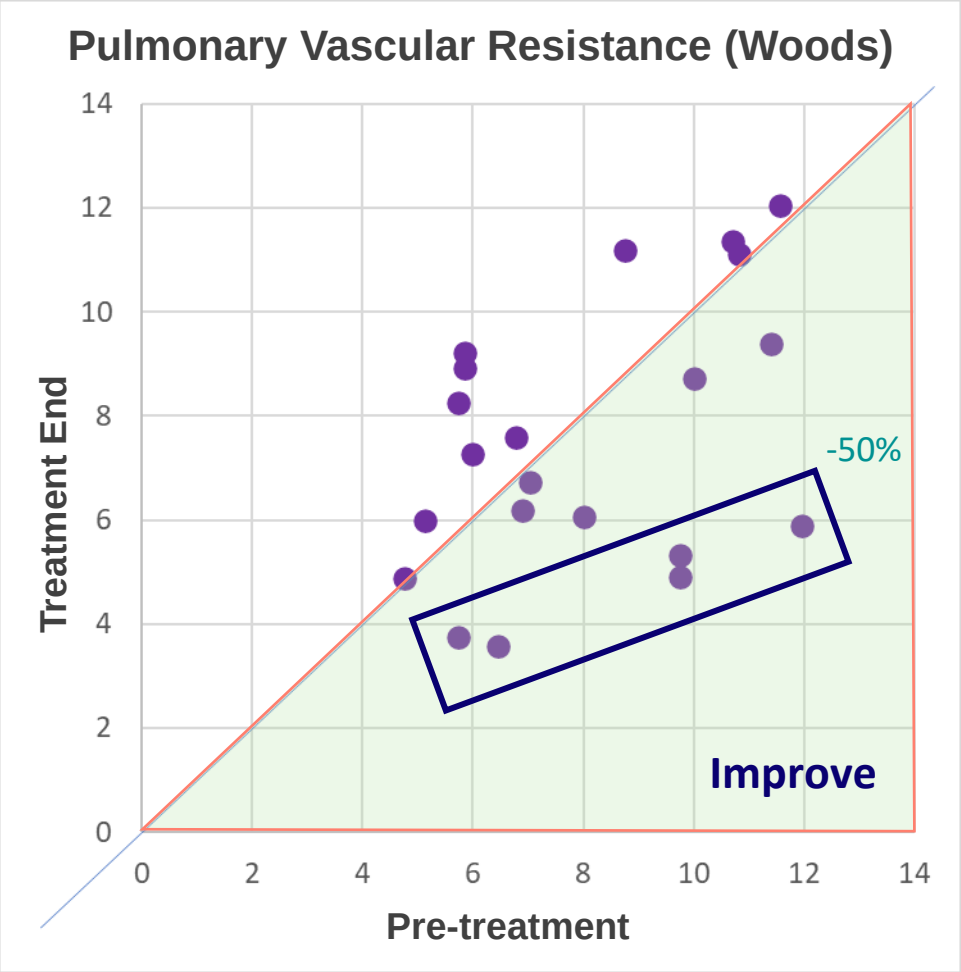
Plexiform Lesions



Cross sections of arteries (<100 µm)

CS014 also reduced small artery-associated fibrosis

CS1 phase IIa trial – Remarkable responders in PVR mostly in low dose group



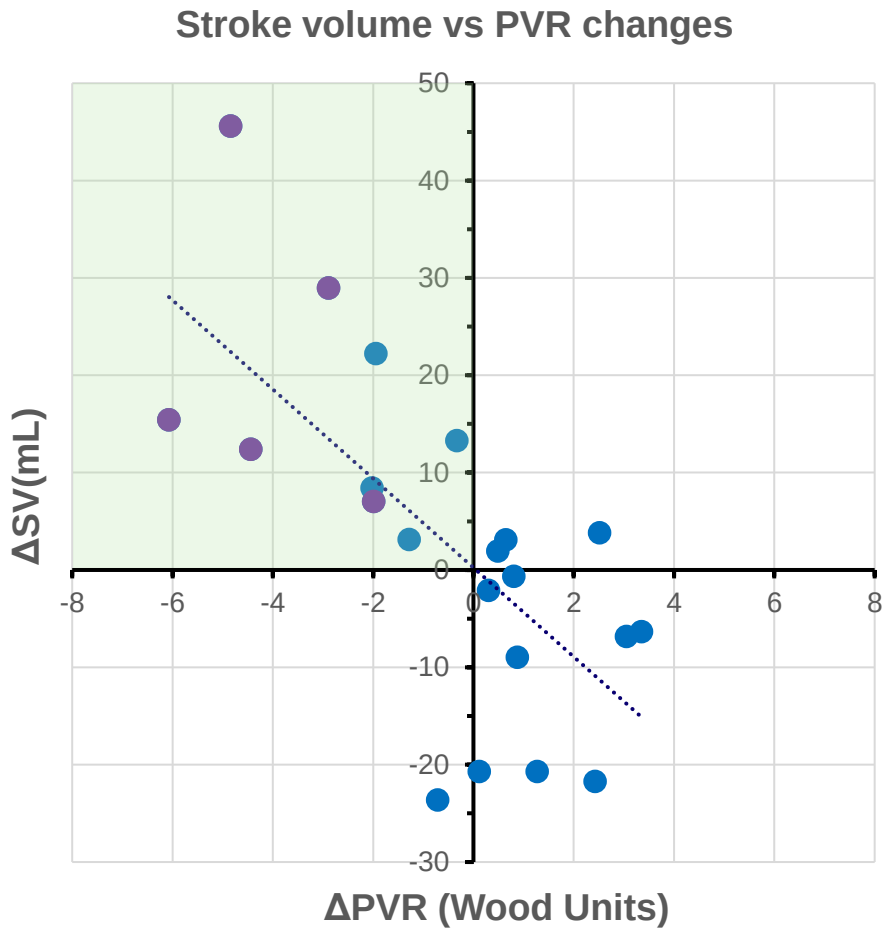
PVR remarkable responders:

- **Reduction in PVR of >30%**
- 5 patients identified, range 35-51% reduction, mean 45%
- 4/5 of the PVR-responders are in low-dose group

PVR reductions of this magnitude have an extremely low probability of occurring by chance*

*Analysis based on STELLAR study placebo data

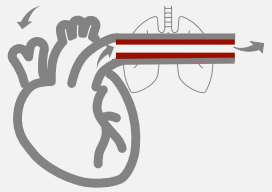
CS1 phase IIa trial – Increased stroke volume associated with reduced PVR in the remarkable responder group



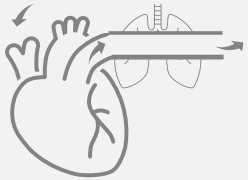
PVR remarkable responders:

- Reduction in PVR and increase in stroke volume
- Clinically meaningful increase in SV: > 10 mL[1]

Impact of PVR on heart function:



Remodeling results in increased PVR and worsened right heart function

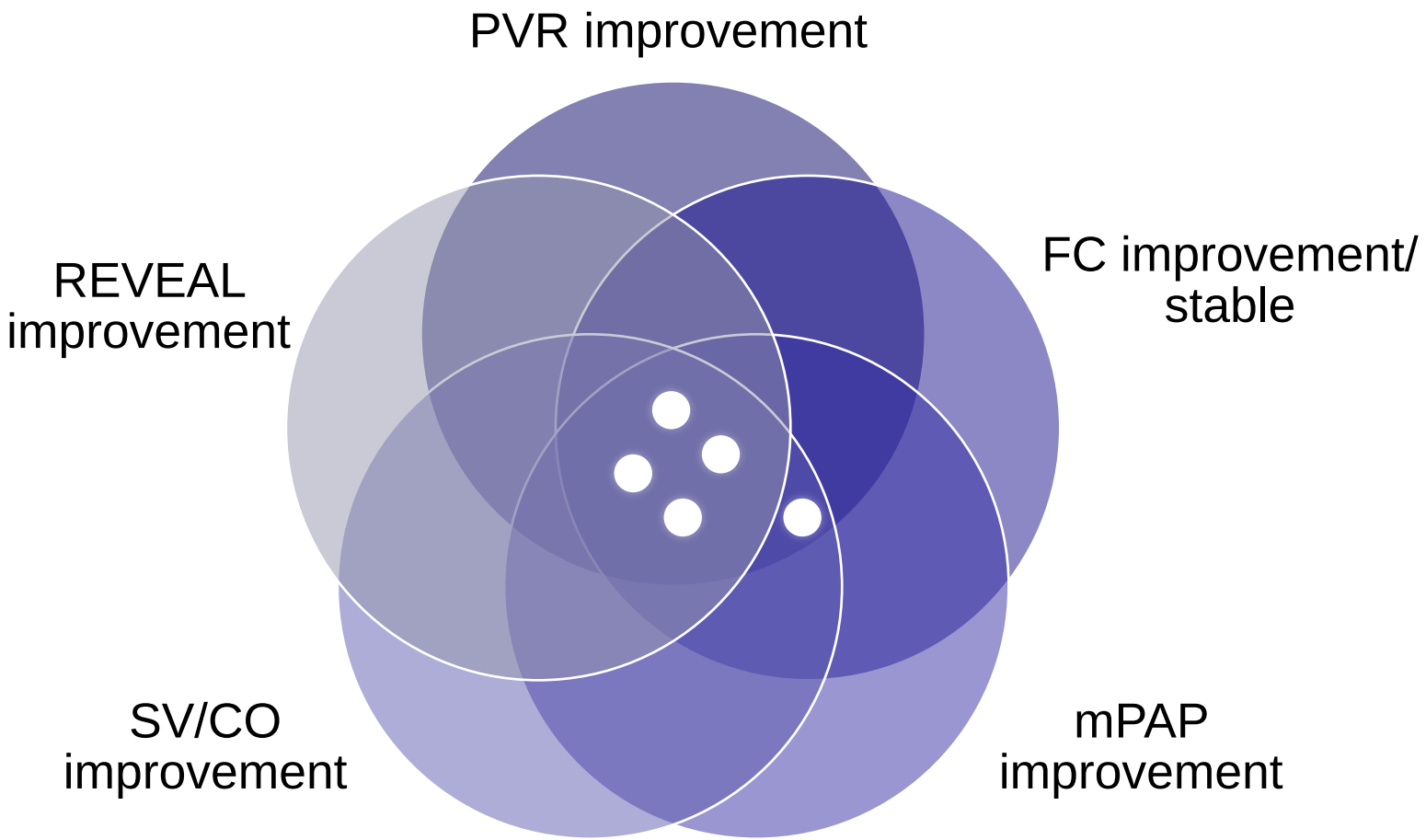


CS1 reduces PVR and improves right heart function

Note: This slide has been updated following the webinar on the 30th of September in order to correct an error.

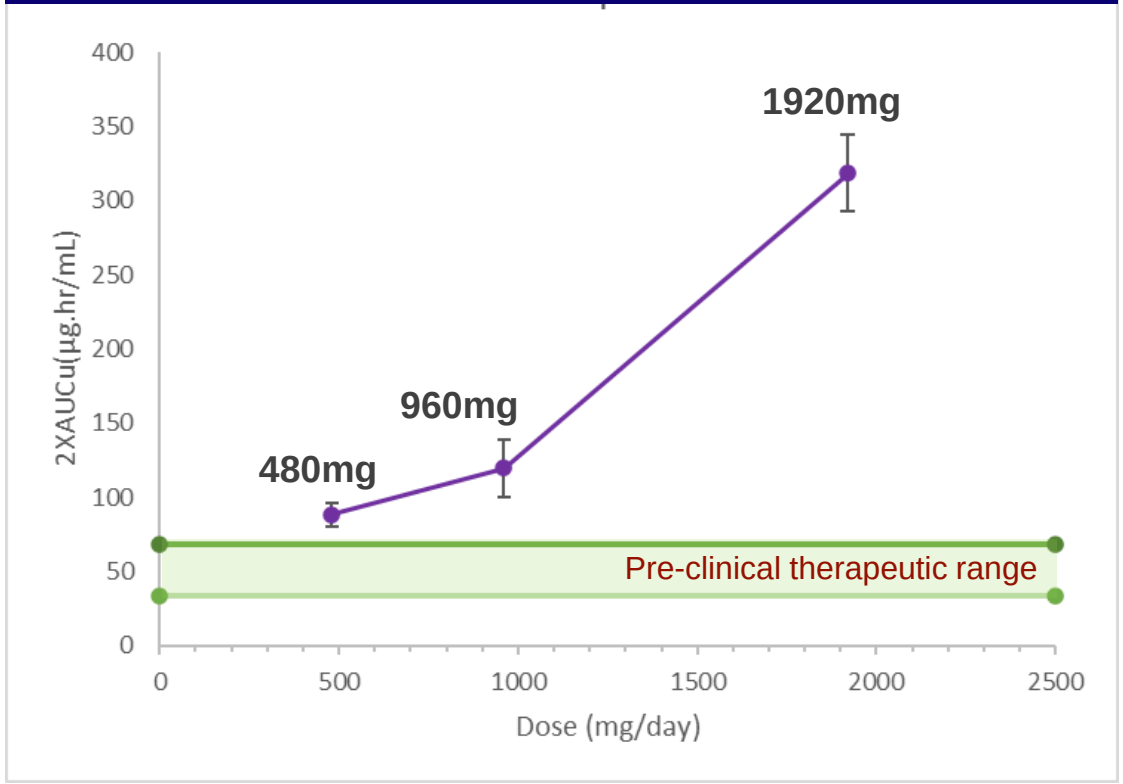
1. Wolferen, Chest 139(5), 2011

Strong alignment between important efficacy parameters among remarkable responders



Overall findings suggest lower dose range optimal

VPA in CS1 patients vs CS014 in preclinical model measured unbound exposures



Preclinical therapeutic range of CS014 is consistent with phase IIa clinical response

- CS014 is an equipotent analog of the active ingredient of CS1
- Maximally effective preclinical unbound exposures approx correspond to low dose levels in our phase IIa clinical trial
- Majority of remarkable PVR-responders are in low-dose group

Summary of in-depth analysis – Evidence of vascular remodeling

- Recently obtained preclinical data with CS014 demonstrates:
  - **Dose-dependent reversal of remodeling** of lung resistance arteries in a PAH model
  - **Dose-dependent reduction of plexiform lesions**
  - **Reduction of fibrosis** associated with pulmonary arteries
  - Maximal efficacy at equivalent exposures to CS1 Ph IIa trial at the low dose
- **24% (5/21)** of the patients **responded to CS1** with **remarkably large reductions in PVR** consistent with the proposed reversal of pathological vascular remodeling
- These **reductions in PVR (35-51%, mean 45%)** were strongly associated with **robust increases in right ventricular stroke volume**
- **These remarkable hemodynamic changes are strongly associated with clinical benefits**

Agenda

Time	Discussion Item	Speaker
13:30	**Welcome**	
13:35	**Introduction to Cereno Scientific**	**Sten R. Sörensen** *CEO, Cereno Scientific*
13:50	**Understanding PAH, a debilitating rare disease**	**Dr. Raymond Benza** *Network Director of Pulmonary Hypertension at Mount Sinai Icahn School of Medicine, New York City*
14:10	**Cereno Scientific's CS1 in PAH**	**Dr. Rahul Agrawal,** *CMO and Head of R&D, Cereno Scientific*
14:15	**Cereno Scientific's CS1 - Phase IIa trial results**	**Dr. Rahul Agrawal,** *CMO and Head of R&D, Cereno Scientific* **Nicholas Oakes,** *Head of Preclinical Development, Cereno Scientific*
14:40	**Investigator and patient perspective of CS1-003 trial**	**Dr. Jason Guichard** *Cardiologist at Prisma Health-Upstate, Assistant Professor of Medicine, University of South Carolina School of Medicine Greenville and investigator in the Phase IIa trial of CS1 in PAH*

Dr. Jason Guichard
Department of Medicine, Division of Cardiology, Prisma Health-Upstate, Assistant Professor of Medicine, University of South Carolina School of Medicine Greenville and investigator in the Phase IIa trial of CS1 in PAH

Investigator and patient perspective of CS1-003 trial

Cereno Scientific

Agenda

Time	Discussion Item	Speaker
14:45	**Next steps for CS1**	**Dr. Rahul Agrawal** *CMO and Head of R&D, Cereno Scientific*
14:55	**Introduction to Fluidda and the innovative Functional Respiratory Imaging technology**	**Jan De Backer** *CEO Fluidda*
15:05	**Short break**	
15:15	**CS014 targeting unmet needs in rare disease IPF**	**Dr. Björn Dahlöf**, *CSO, Cereno Scientific*
15:35	**CS585 being evaluated rare diseases**	**Dr. Michael Holinstat** *Prof. at University of Michigan Medical School; and Director Translation Research, Cereno Scientific*
15:55	**Cereno Scientific - strategic priorities and future outlook**	**Sten R. Sörensen** *CEO, Cereno Scientific*
16:10	**Questions from Audience on site and online**	Moderated by Dr. Rahul Agrawal, *CMO and Head of R&D, Cereno Scientific*
16:25	**Concluding remarks**	**Sten R. Sörensen** *CEO, Cereno Scientific*

Dr. Rahul Agrawal
CMO and Head of R&D

Next steps for CS1

Cereno Scientific

CS1 PAH – Path forward

- Expanded Access Program and long-term data
- Completing the analysis of the trial
- Regulatory path
- Fluidda study

Cereno Scientific

Perceived treatment benefits prompted investigators to request expanded access to CS1 for study participants

FDA accepted protocol – Jan 30th, 2024

"Patient has derived benefit from CS1 treatment in parent study CS1-003 based on the investigator's judgement and the benefit of continued CS1 treatment outweighs the risk or the patient could benefit from continued treatment with CS1"

- CS1-004 Protocol

First patient dosed in August 2024

"Compassionate use allows patients to continue CS1 for their treatment of PAH, and to continue to experience the quality-of-life improvements perceived by the patients and clinicians."

Dr Raymond Benza,
Global thought leader PAH, Network Director of Pulmonary Vascular Disease at Mount Sinai Icahn School of Medicine, New York City; Principal Investigator for CS1 Phase 2 Study,

Source: Cereno Press Release – Compassionate Use Program, Released on March 06, 2024

CS1 – Clear path forward to develop asset as a disease-modifying therapy for PAH

- Expanded access program (compassionate use) ongoing and will provide long-term data
- Complete analysis of the PAH trial
- Regulatory path
  - Engaging with regulatory authorities for pivotal trial
- Fluidda partnership to document the impact of CS1 on reverse remodeling of pulmonary arteries

Cereno signs agreement with Fluidda to evaluate the impact of CS1 on reverse remodeling in a clinical setting

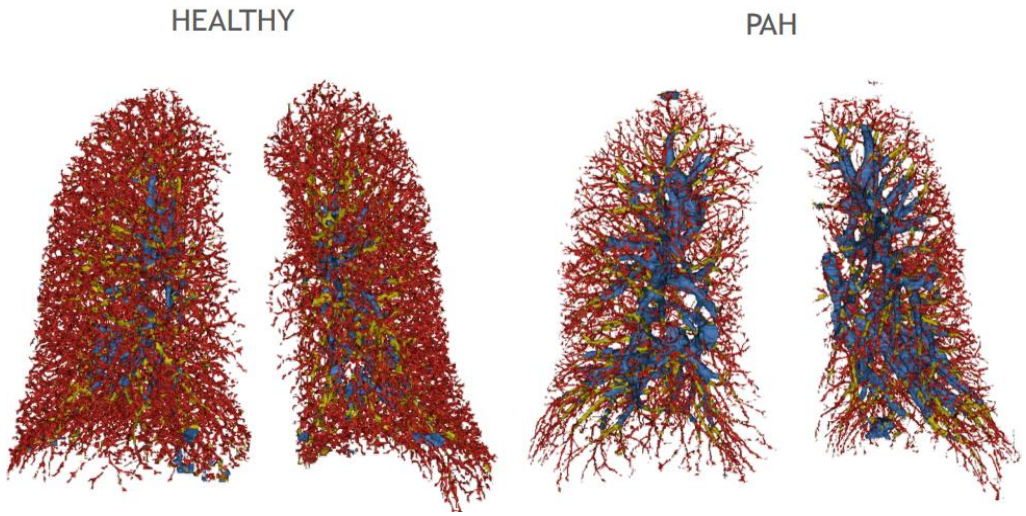
Press release
September 30, 2024

Cereno Scientific

Cereno Scientific signs agreement with Fluidda, to evaluate the impact of its HDAC inhibitor CS1 on reverse remodeling of pulmonary vessels in patients with PAH

Cereno Scientific (Nasdaq First North: CRNO B), a pioneering biotech developing innovative treatments for rare and common cardiovascular disease, today announced that the Company has signed an agreement with medical technology company Fluidda on Respiratory Imaging solutions, with the aim to visualize signs of reverse remodeling of lead drug candidate CS1 in Pulmonary Arterial Hypertension (PAH) in a clinical setting.

"We have a vision to develop new therapies which address the root cause of cardiovascular disease as we believe this will provide high value to patients with respect to improvement of quality of life and survival. On the heels of our increasing knowledge of impact of reverse remodeling capacity of HDACi from our preclinical program CS014, together with our top line results from our Phase IIa study with our lead HDACi program CS1, I am excited to announce our partnership with Fluidda. This collaboration will allow Cereno to use Fluidda's cutting-edge technology to visualize CS1's ability for long-term reverse remodeling in PAH patients," **said Sten R. Sörensen, CEO, Cereno Scientific**



Source: FLUIDDA company presentation

Agenda

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15:35	**CS585 being evaluated rare diseases**	**Dr. Michael Holinstat** *Prof. at University of Michigan Medical School; and Director Translation Research, Cereno Scientific*
15:55	**Cereno Scientific - strategic priorities and future outlook**	**Sten R. Sörensen** *CEO, Cereno Scientific*
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16:25	**Concluding remarks**	**Sten R. Sörensen** *CEO, Cereno Scientific*

Jan De Backer
Fluidda, Chief Executive Officer

Introduction to Fluidda and the innovative Functional Respiratory Imaging technology

Cereno Scientific

FLUIDDA

Functional Respiratory Imaging for Evaluating Pulmonary Vascular Treatment Responses

Jan De Backer, PhD MBA
CEO

FUNCTIONAL RESPIRATORY IMAGING

FLUIDDA

1. CT SCAN

CONVENTIONAL
CT ANALYSES

2. VISUAL READ

FUNCTIONAL RESPIRATORY IMAGING

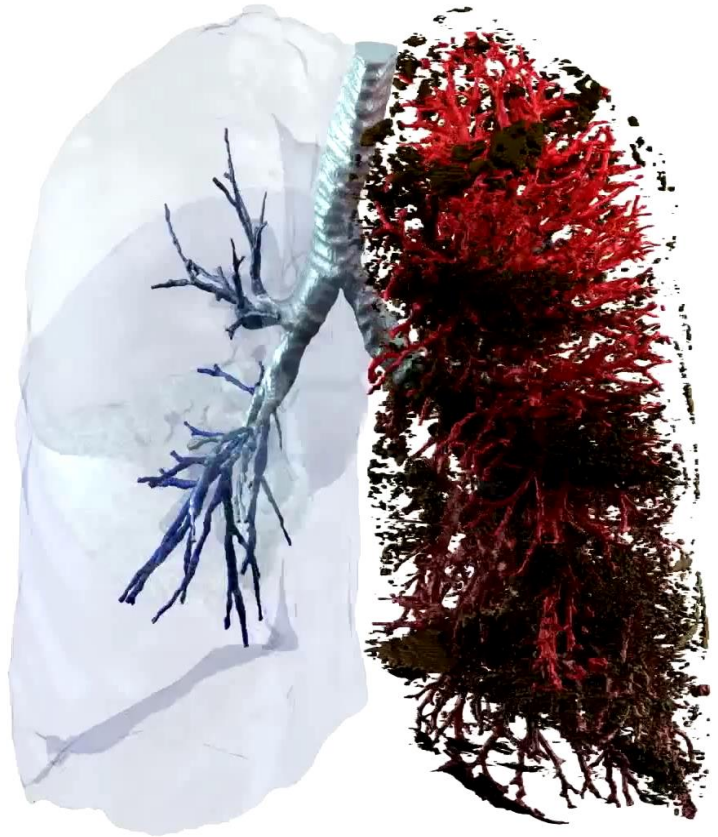
FLUIDDA

1. CT SCAN

2. CLOUD UPLOAD

FUNCTIONAL RESPIRATORY IMAGING (FRI)

3. REPORTS



FUNCTIONAL RESPIRATORY IMAGING

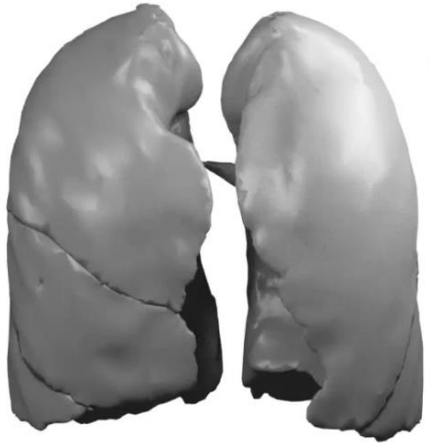
FLUIDDA

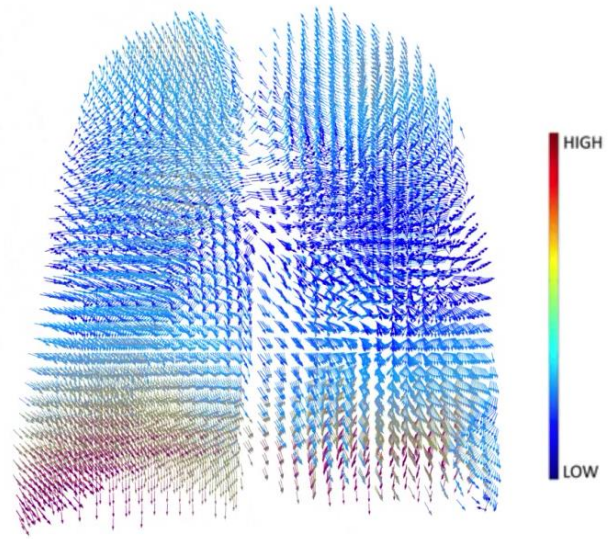
1. CT SCAN

2. CLOUD UPLOAD

3. REPORTS

FUNCTIONAL RESPIRATORY IMAGING (FRI)

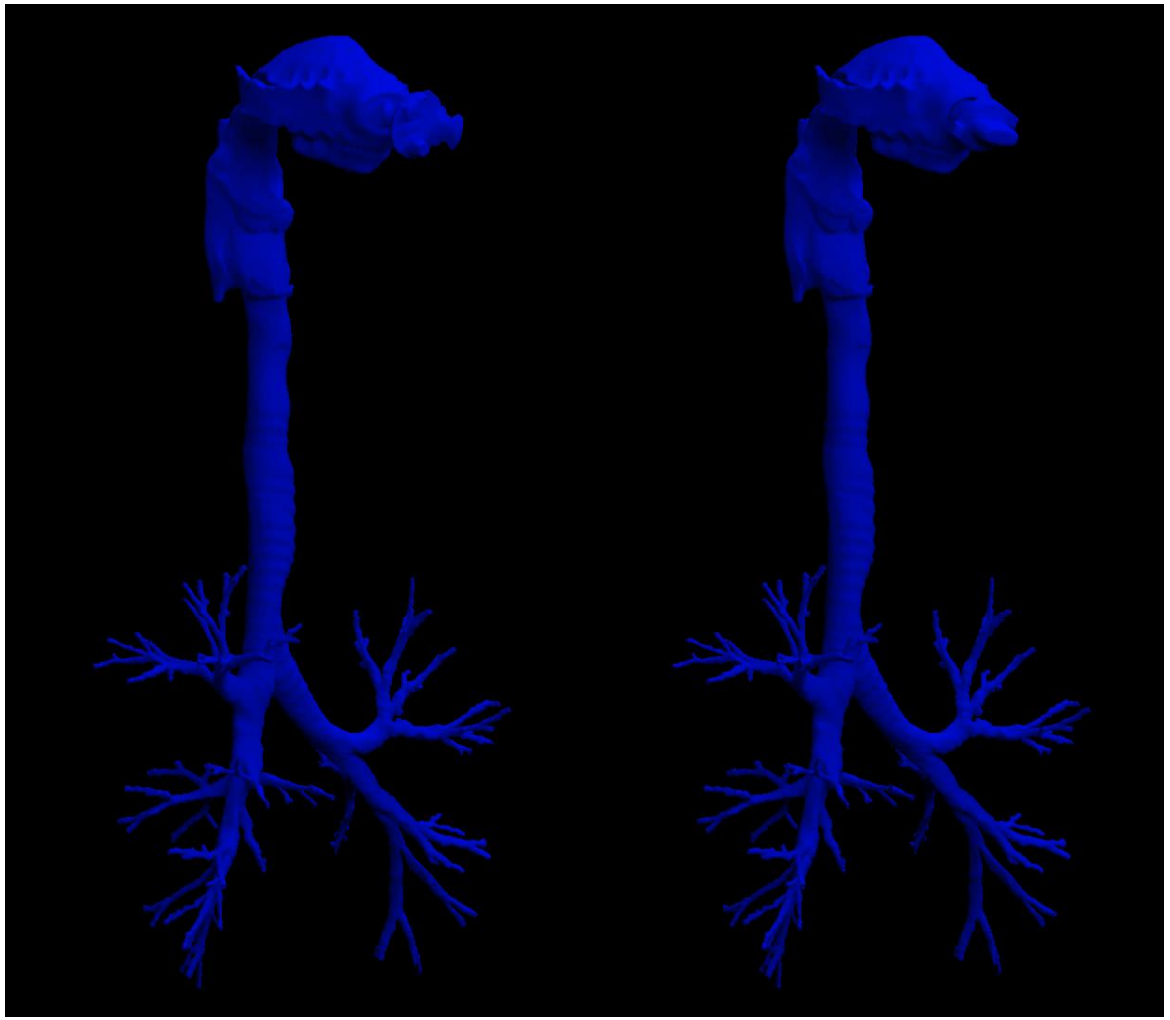


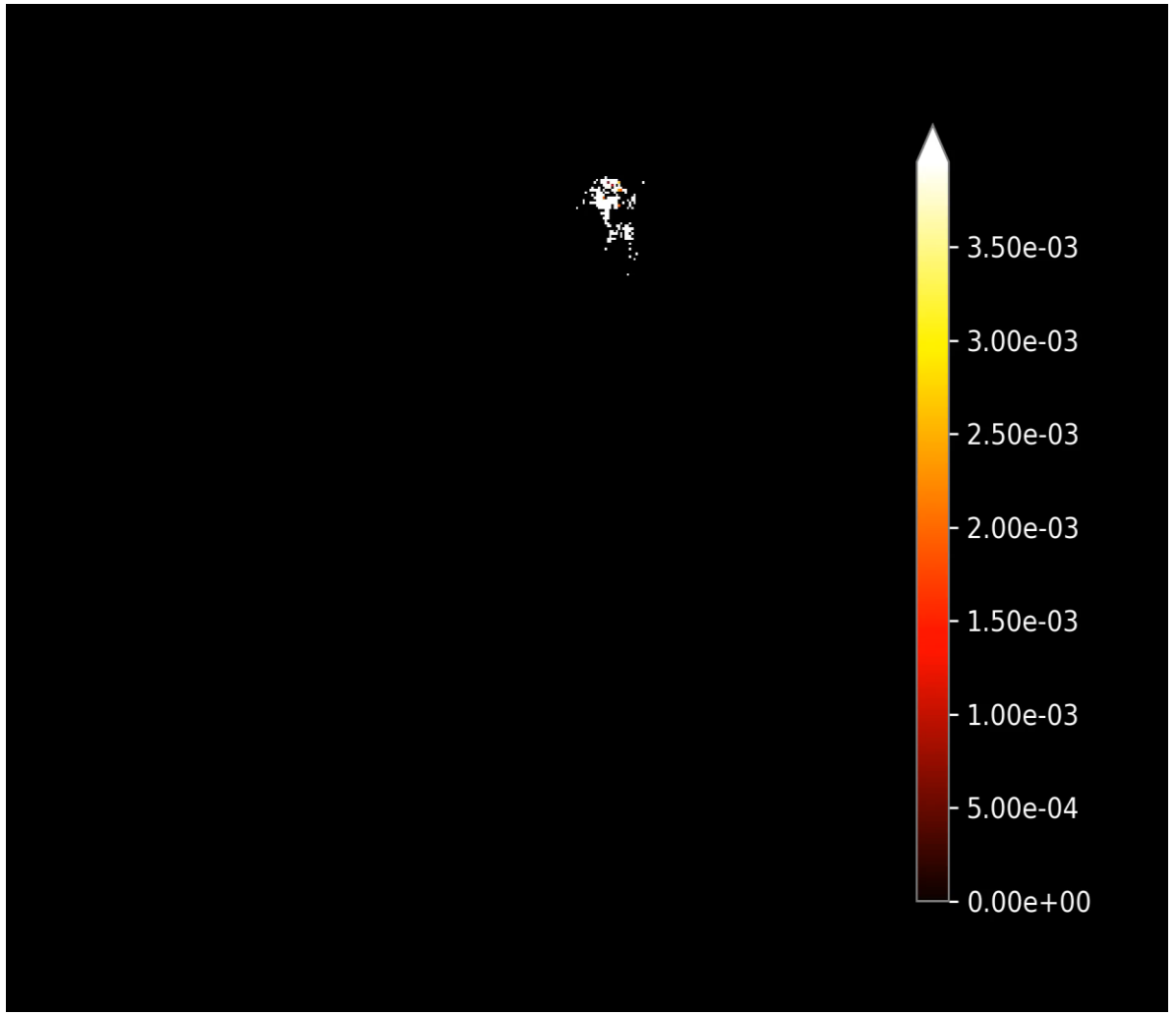


AEROSOL DEPOSITION

FRI yields drug deposition without the need for radiolabeling

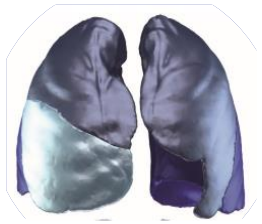
FLUIDDA



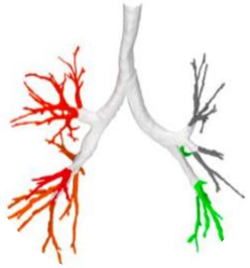


FRI PROVIDES COMPREHENSIVE SET OF QUANTITATIVE OUTCOME PARAMETERS

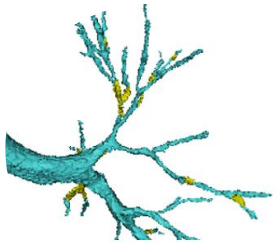
FLUIDDA



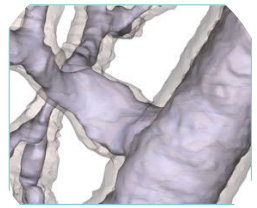
Lung Volumes



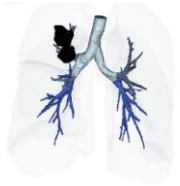
Airway Volumes



Mucus plugs

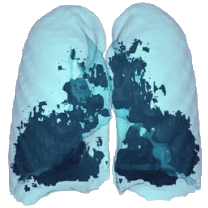


Airway Wall Thickness



Nodules

LUNG & AIRWAY STRUCTURE

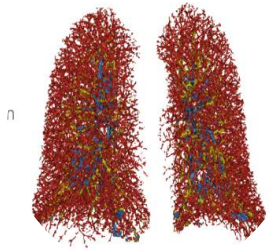


Emphysema

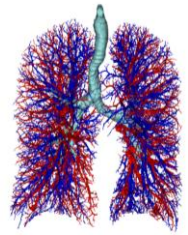
Air Trapping

Fibrosis

PARENCHYMAL STRUCTURE

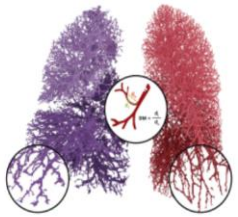


Blood Volume Distribution



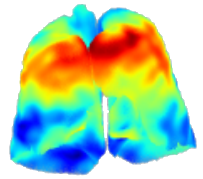
Arteries Veins

Blood Vessel Wall Thickness

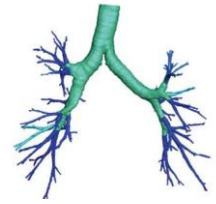


Vessel Tortuosity

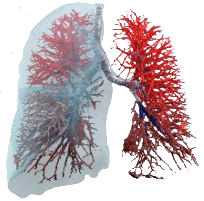
BLOOD VESSELS STRUCTURE



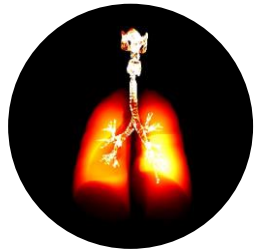
Ventilation



Airway Resistance



Ventilation/ Perfusion



Aerosol Deposition

PULMONARY FUNCTION

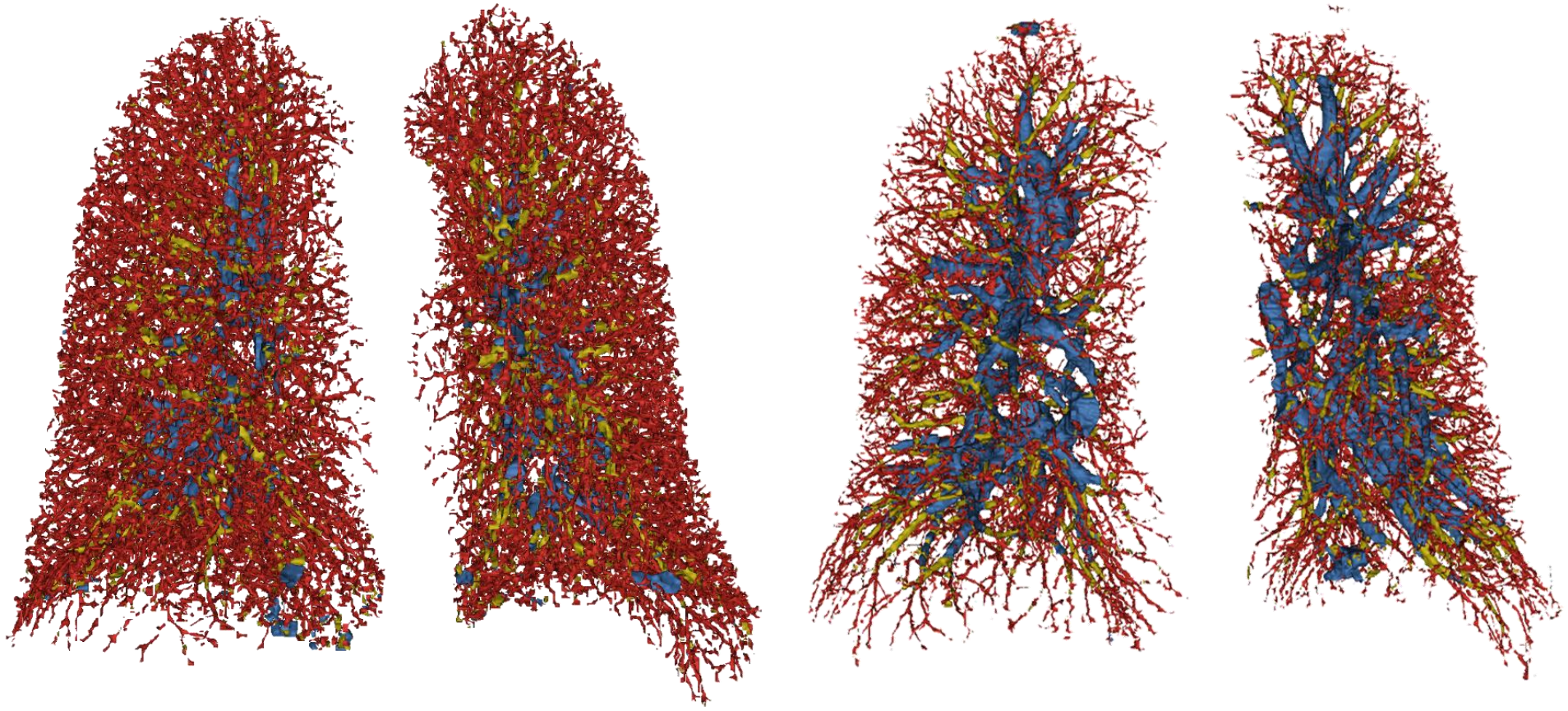
BLOOD VESSEL VOLUME MEASUREMENTS (BVX)

A tool for research in pulmonary hypertension

FLUIDDA

HEALTHY

PAH



SIGNATURE OF PAH

Redistribution of vascular volume to larger vessels

- 10 matched patients per arm:
  - Normalized by total pulmonary vascular volume
- Significant reductions in BV5
- Significant increases in BV10

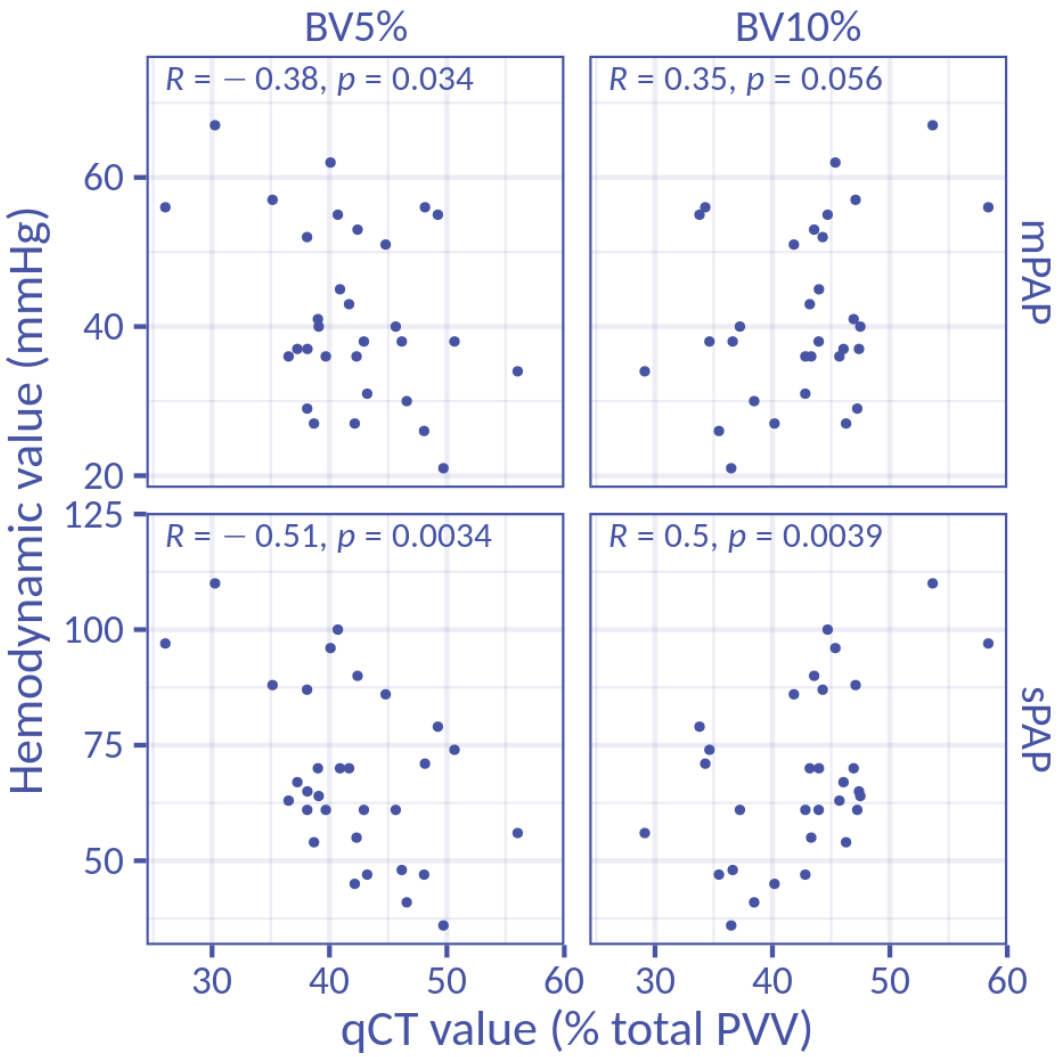
Small blood vessel volume (BV5)

Large blood vessel volume (BV10)

SIGNATURE OF PAH

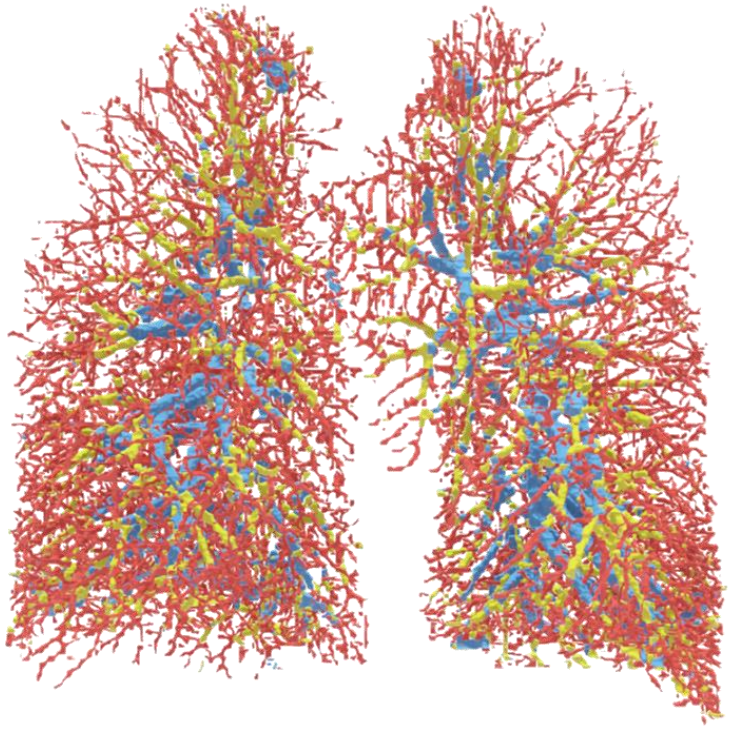
Association between vascular volumes and pulmonary hemodynamics

- **31 subjects with PAH** studied retrospectively in collaboration with The Ottawa Heart Institute
  - Scans were SoC (diverse settings)
  - Etiology of PAH was varied
- **BV5**
  - Significant negative associations with mPAP
- **BV10**
  - Significant positive associations with mPAP
- Associations with sPAP were stronger, reflecting the role of peak pulmonary artery pressures in distention of proximal arteries

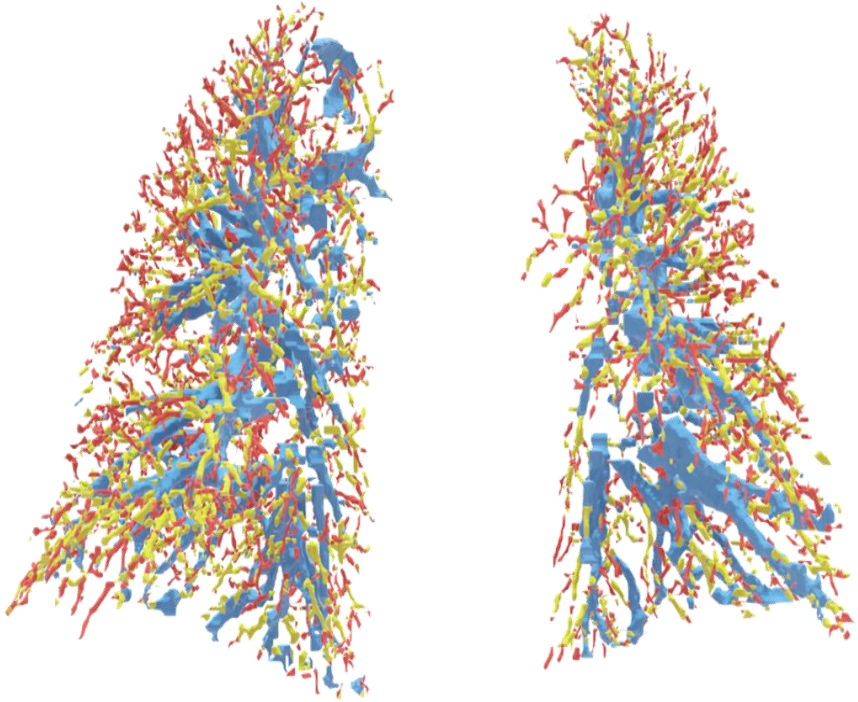


PULMONARY VASCULATURE
IN COPD, COPD-PH

COPD



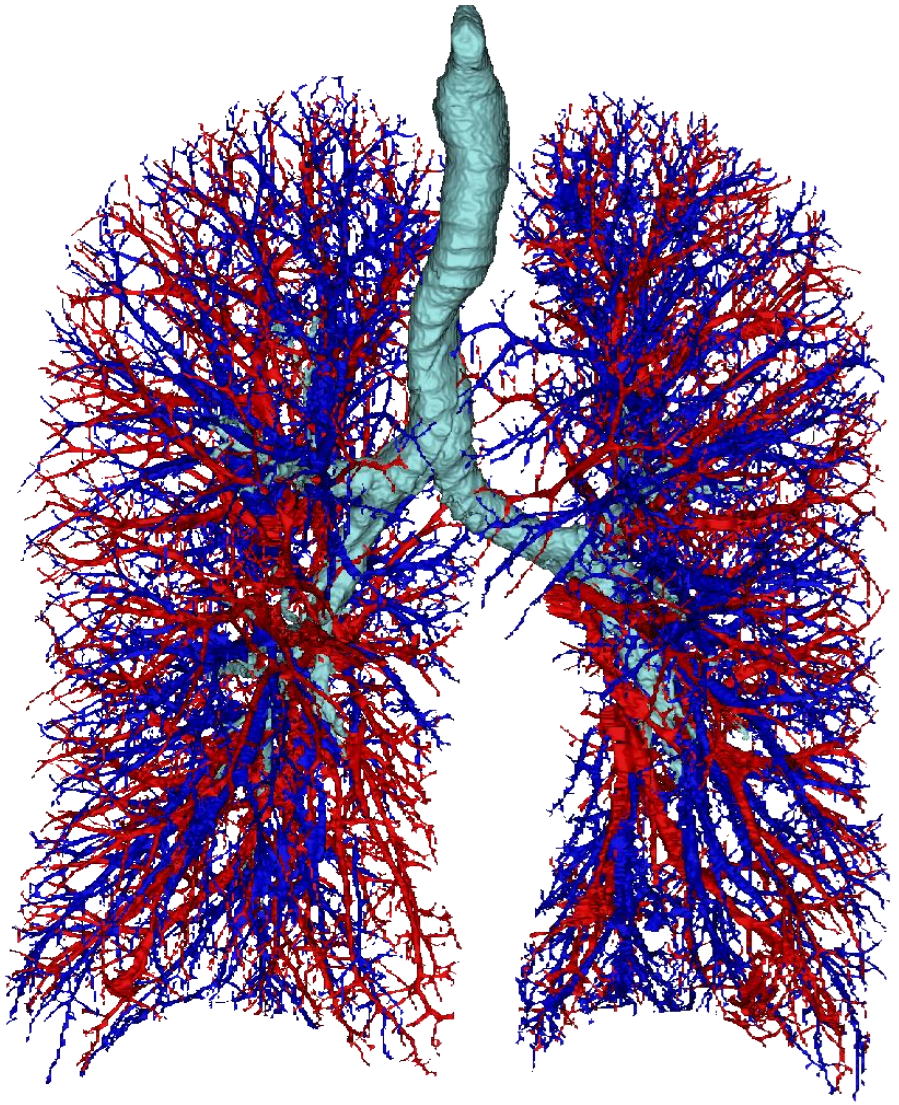
COPD-PH



ARTERIES-VEINS SEPARATION

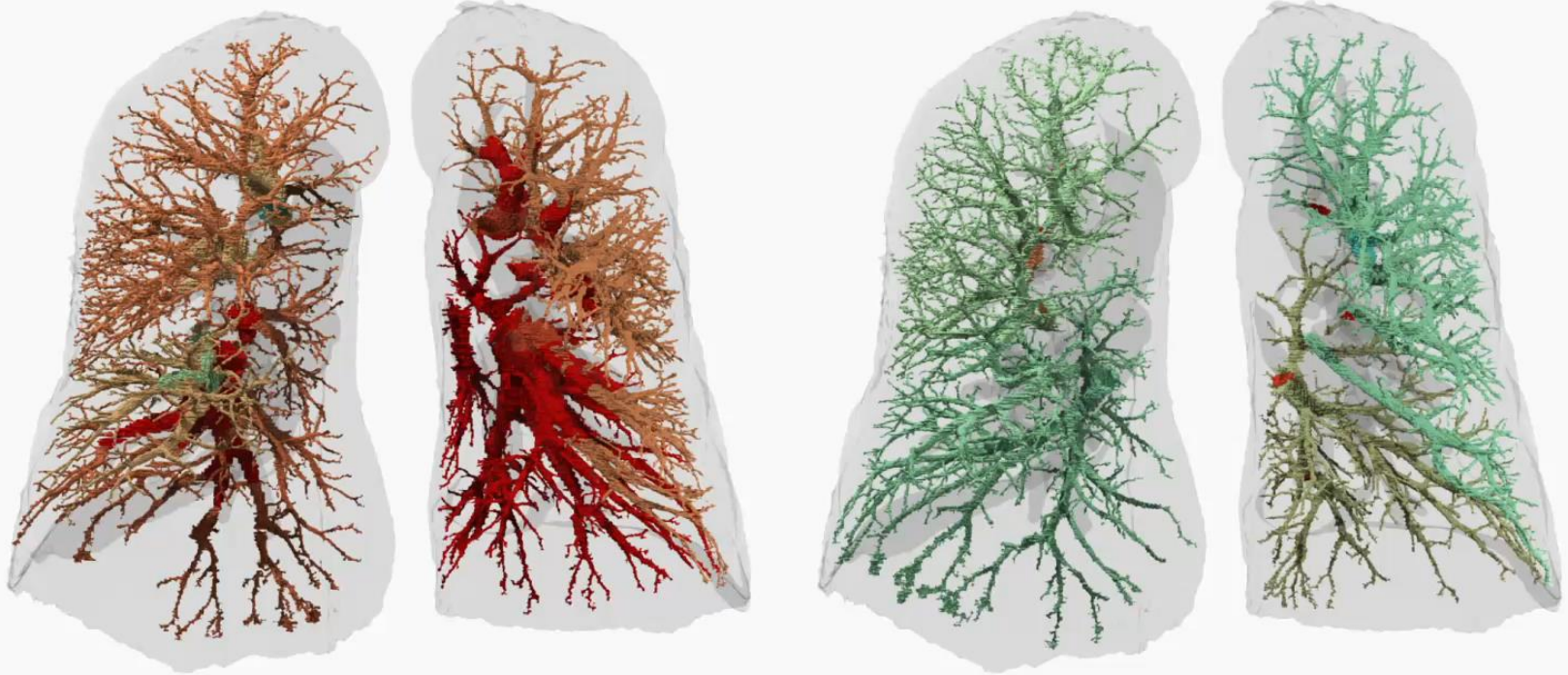
Separation of the veins (blue) and arteries (red)

- **AI enabled process:** Separates vascular volumes (BVX) into arteries and veins.
- **BV5 findings:**
  - Both arterial and venous BV5 are reduced in PAH patients compared to healthy volunteers.
  - Arterial differences are more pronounced than venous differences.
- **BV10 findings:**
  - Only arterial BV10 is significantly higher in PAH patients compared to healthy volunteers.
- May enable **improved phenotyping** of post-capillary involvement.



BLOOD VESSEL WALL THICKNESS

PAH vs healthy



OVERVIEW FRI STUDIES IN PULMONARY HYPERTENSION

- **Cereno Scientific**
  - CS1 in subjects with PAH
- **Merck**
  - MK-5475 in subjects with PAH
  - MK-5475 in subjects PH-COPD
  - MK-5475 in healthy volunteers
- **Gossamber Bio**
  - Seralutinib in PAH (TORREY)
  - Seralutinib in PAH (Prosera)
- **Liquidia**
  - Treprostinil DPI in PH-ILD (ASCENT)
- **Insmed**
  - Treprostinil palmitil inhalation powder in PH-ILD
  - Treprostinil palmitil inhalation powder in PAH
- **Pulmovant**
  - Mosliciguat in PH-ILD
- **Johnson and Johnson/Actelion**
  - Selexipag in healthy volunteers
- **Bellerophon**
  - Pulsed iNO in PH-COPD
  - Pulsed iNO in PH-COPD and PH-ILD

FLUIDDA has trained **>550 clinical sites** worldwide on the use of FRI in clinical trials.

Agenda

Time	Discussion Item	Speaker
14:45	**Next steps for CS1**	**Dr. Rahul Agrawal** *CMO and Head of R&D, Cereno Scientific*
14:55	**Introduction to Fluidda and the innovative Functional Respiratory Imaging technology**	**Jan De Backer** *CEO Fluidda*
15:05	**Short break**	
15:15	**CS014 targeting unmet needs in rare disease IPF**	**Dr. Björn Dahlöf**, *CSO, Cereno Scientific*
15:35	**CS585 being evaluated rare diseases**	**Dr. Michael Holinstat** *Prof. at University of Michigan Medical School; and Director Translation Research, Cereno Scientific*
15:55	**Cereno Scientific - strategic priorities and future outlook**	**Sten R. Sörensen** *CEO, Cereno Scientific*
16:10	**Questions from Audience on site and online**	Moderated by Dr. Rahul Agrawal, *CMO and Head of R&D, Cereno Scientific*
16:25	**Concluding remarks**	**Sten R. Sörensen** *CEO, Cereno Scientific*

Short Break

- 10 min

Cereno Scientific

Agenda

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Dr. Björn Dahlöf
Chief Executive Officer

CS014 targeting unmet needs in rare disease IPF

Cereno Scientific

Cereno's portfolio is uniquely positioned to make impact in diseases with high unmet medical needs

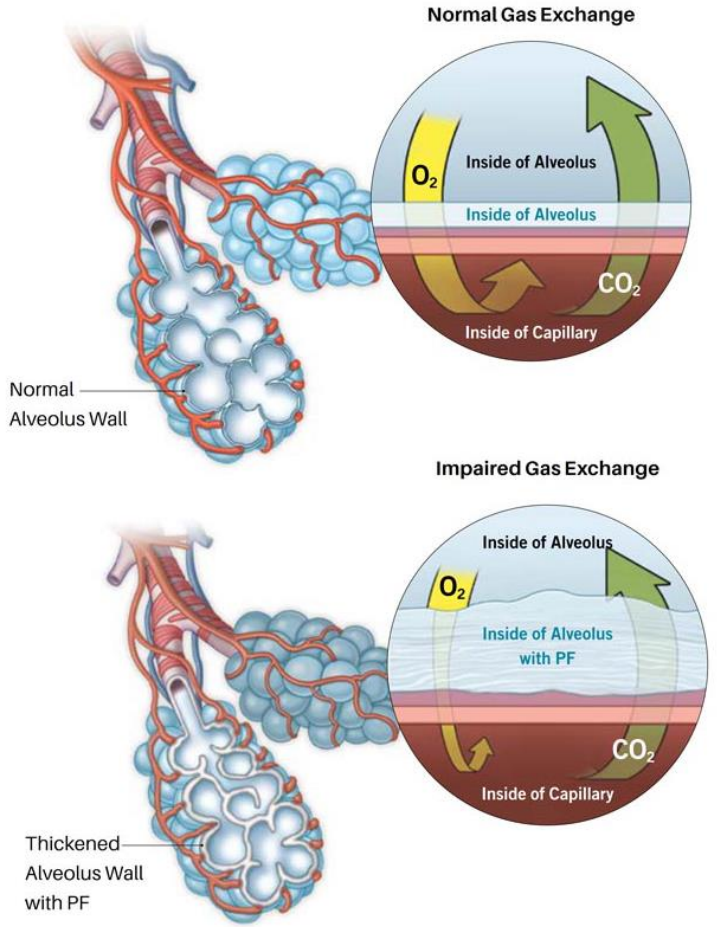
Program	Target	Indication	Preclinical	Phase I	Phase II	Phase III	Status
CS1	HDACi with disease-modifying potential	PAH					Phase II top-line results in Q3 2024[1] Expanded Access Program initiated in Q1 2024[1]
CS014	HDACi with disease-modifying potential	IPF					Phase I initiated in Q2 2024[2]
CS585	PRA oral, selective and potent	CVD					Ongoing preclinical development during 2024/25

Note: Progress bars are only an estimation, not to scale.

Source: 1. Cereno Press Release, 21st Feb 2024; 2. Cereno Press Release, 18th June 2024

IPF is a devastating disease with a huge unmet medical need

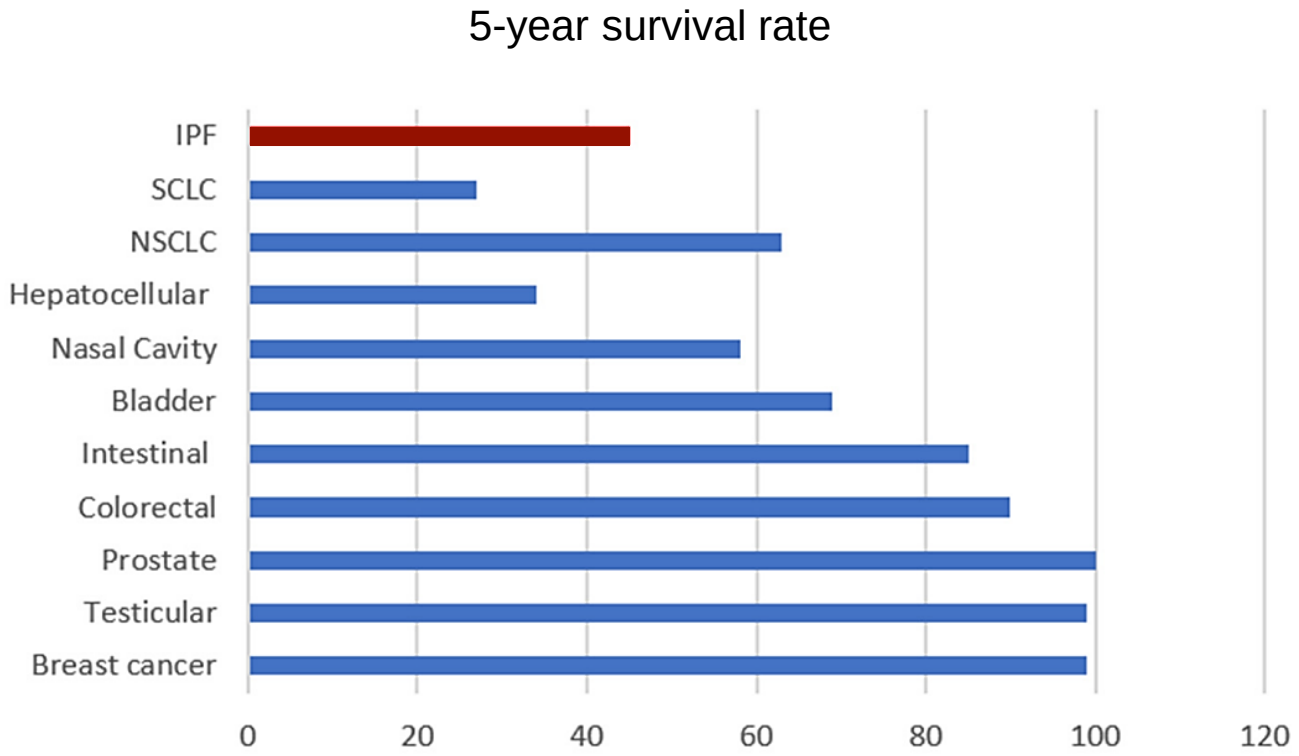
- **Idiopathic pulmonary fibrosis (IPF)** is a **chronic fibrotic lung disease** characterized by **dry cough, fatigue**, and **progressive exertional dyspnea**
  - **Lung parenchyma** and structure are **destroyed**
  - **Loss of lung compliance**
  - **Gas exchange** becomes **compromised**
- The disease progresses to **respiratory failure**
- **Death** typically occurs **within 3 to 5 years of diagnosis**



Sources: Glass, D., et al., Clin Resir J., 2022; Raghu, G., et al., Am J Respir Crit Care Med, 2022; Pulmonary Fibrosis Foundation (PFF).

IPF has worse prognosis than many cancers

Cancer Survival vs IPF

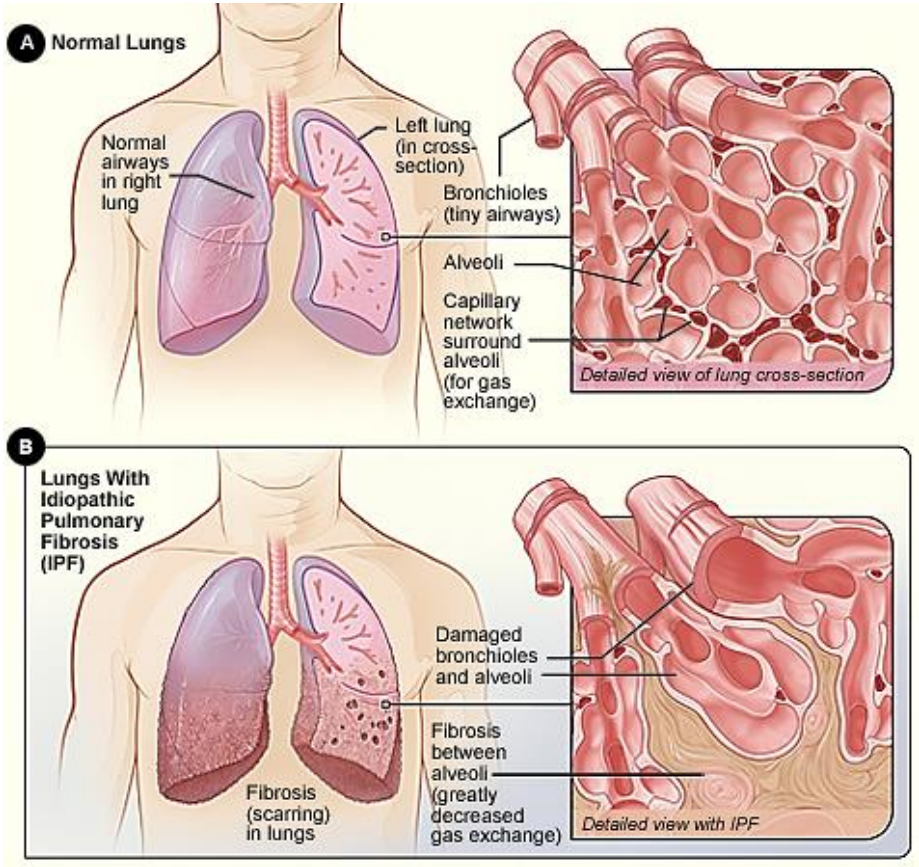


- IPF has a **poor prognosis**, with only around **45% of patients** surviving **five years** after diagnosis
- This survival rate is **worse than that of many types of cancer**, emphasizing the severity of the disease and the challenges associated with its management and treatment

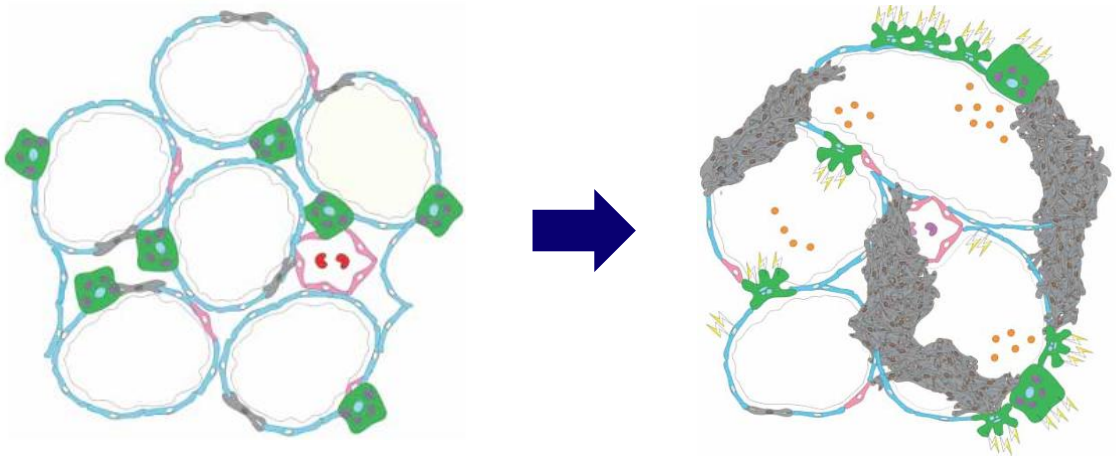
SCLC: Small cell lung cancer. NSCLC: Non-small cell lung cancer.

Source: Wu, B., et al., Cancers, 2022.

IPF is characterized by irreversible scar tissue generation and progressive deterioration of pulmonary function



Healthy Lung	IPF Lung

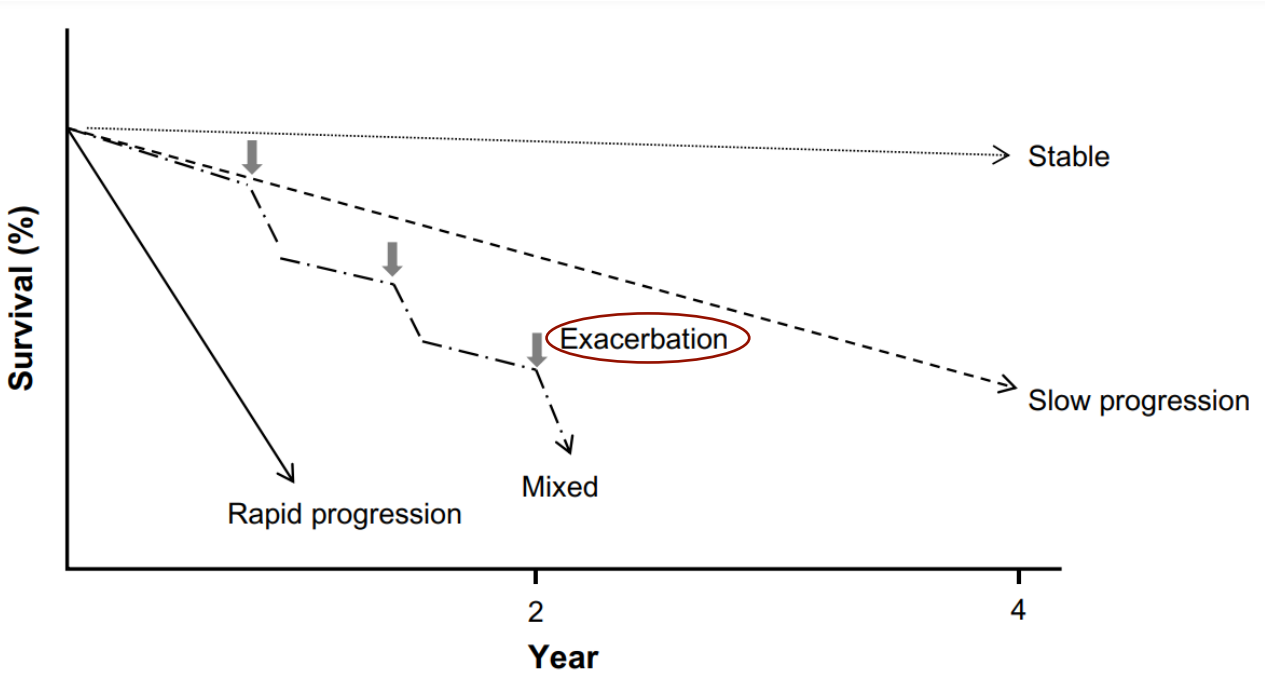


Abnormal fibroblast proliferation, myofibroblast differentiation and irreversible scar tissue generation, with oxidative stress contributing to this process

Sources: Korfei, et al., Eur Resp Rev, 2020. Figures: Adapted from NIH and Korfei et al., 2020.

IPF symptoms include dyspnea and dry persistent cough, with acute and severe respiratory exacerbations

Dyspnea, dry & persistent cough, inspiratory crackles, finger clubbing, acute respiratory exacerbations

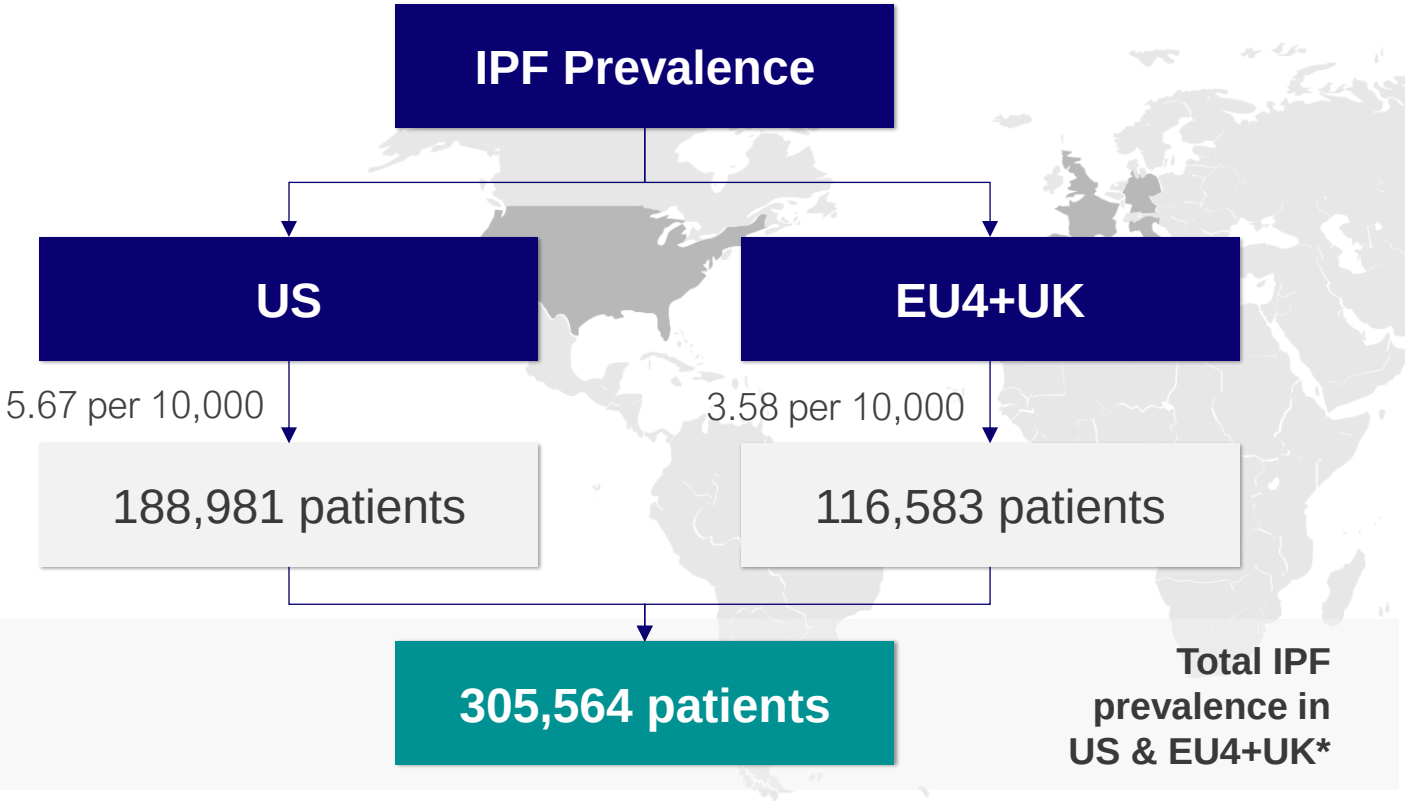


High-resolution computed tomography (HRCT) demonstrates a usual interstitial pneumonia (UIP) pattern

Sources: Raghu, G., et al., Am J Respir Crit Care Med, 2022; Murphy B., Rare Disease Advisor, 2021 Pulmonary Fibrosis Foundation (PFF); Fujimoto, H., et al., Circulatory, Respiratory and Pulmonary Medicine, 2015; pulmonaryfibrosismd.com.

IPF is a rare disease, with 305,564 patients affected in the US & EU4+UK

PREVALENCE OF IDIOPATHIC PULMONARY FIBROSIS - US & EU4+UK



- The broad definition used in some cases makes the population quite large.
- However, IPF meets the rare disease threshold for **orphan drug designation** both in the US and Europe.

61-70%

Of IPF patients are treated with at least one anti-fibrotic drug

*Including broad definition of IPF, i.e., patients that are diagnosed without precise diagnostic procedures

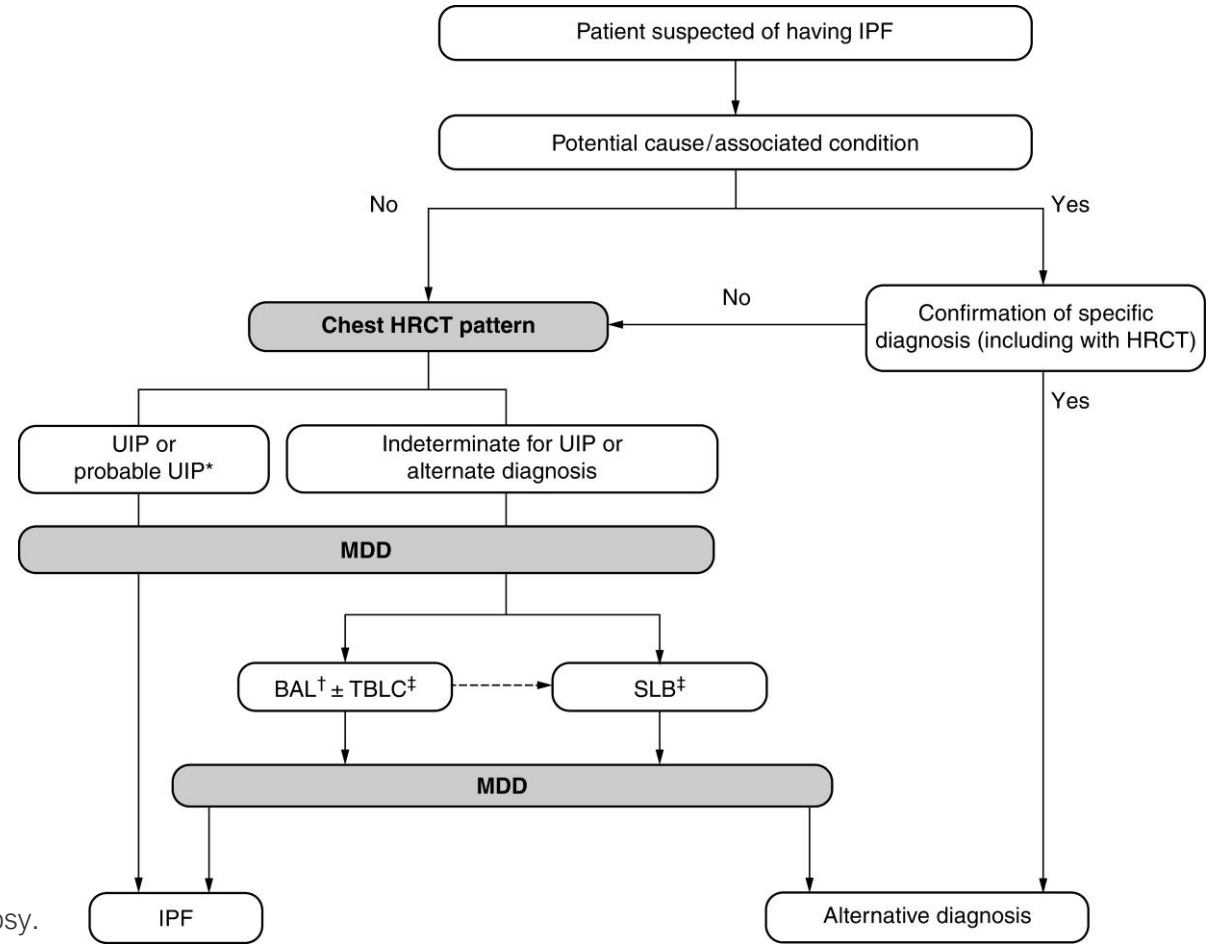
Cereno Scientific

Sources: Salisbury et al., Ann Am Thorac Soc, 2020; Holtze et al. Respir Res, 2020; Maher et al., Respir Res, 2021.

IPF diagnosis can be confirmed on high-resolution computed tomography

Diagnosis:

- IPF **diagnosis can be made based on high-resolution computed tomography** (HRCT) and **biopsy or BAL**
- However, patients with a radiological pattern of probable usual interstitial pneumonia (UIP) can receive a diagnosis of IPF after multidisciplinary discussion (MDD) without confirmation by lung biopsy



BAL: Bronchoalveolar lavage. TBLC: Transbronchial lung cryobiopsy. SLB: Surgical lung biopsy.

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Sources: Raghu, G., et al., Am J Respir Crit Care Med, 2022; Maher et al., Respir Res, 2021.

IPF treatment options are limited and include only two drug treatments

IPF Treatment Guideline

Pharmacological:

- **Nintedanib**
- **Pirfenidone**

Non-pharmacological:

- Oxygen supplementation[1]
- Pulmonary rehabilitation

Comorbidities:

- Pulmonary hypertension
- Gastroesophageal reflux
- Obstructive sleep apnea
- Lung cancer

Symptom control:

- Palliative care

If increased risk of mortality, evaluate for lung transplantation at diagnosis.

MONITOR FOR DISEASE PROGRESSION

Consider pulmonary function testing and 6MWT every 4–6 months or sooner if clinically indicated

Consider annual HRCT if clinical suspicion of worsening or risk of lung cancer

Consider an HRCT if there is concern for an acute exacerbation

Consider a CT pulmonary angiogram if clinical concern for pulmonary embolism

Acute exacerbations:
• Corticosteroids

1. If hypoxemic.

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Sources: Raghu, G., et al., Am J Respir Crit Care Med, 2022.

Poor tolerability and modest impact on disease progression lead to demand for better treatments for IPF

	Pirfenidone (Esbriet)	Nintedanib (OFEV)
Mechanism of action	Inhibits fibroblast production, likely through regulation of TGFβ	Intracellular tyrosine kinase inhibitor
Efficacy in clinical trials	Benefit on FVC decline over 1 year Relative benefit observed on death or disease progression (mainly FVC), but not on dyspnea or mortality	The treatment group showed ~50% less decline in FVC compared with placebo. Acute exacerbation reduced in one trial but not the other, and trend toward improve QoL
Safety profile	**Gastrointestinal symptoms** (primarily nausea), **rash** and **photosensitivity** were 2-6-times more common with pirfenidone than placebo	**Diarrhea** ~2/3 of patients, **nausea, vomiting**, and **weight loss** Around **20–25% of patients unable to tolerate** nintedanib

Neither nintedanib nor pirfenidone is associated with a consistent improvement in patient-centered outcomes such as symptoms, 6-min walk distance, day-to-day functioning, fatigue or mortality.

FVC: Forced vital capacity

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Source: Bonella, F. et al., Drugs, 2023.

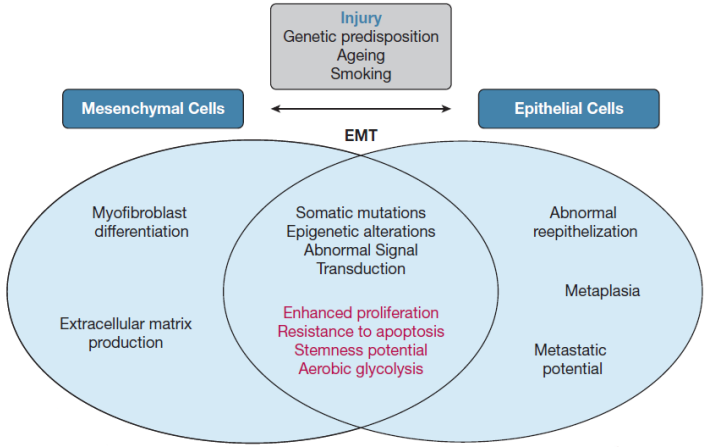
Comorbidities: IPF is strongly associated with VTE and lung cancer

[Translating Basic Research Into Clinical Practice]

CHEST

Common Pathogenic Mechanisms Between Idiopathic Pulmonary Fibrosis and Lung Cancer

Argyris Tzouvelekis [1], Georgia Gomatou [2], Evangelos Bouros [1], Rodoula Trigidou [3], Vasilios Tzilas [1], Demosthenes Bouros [4]



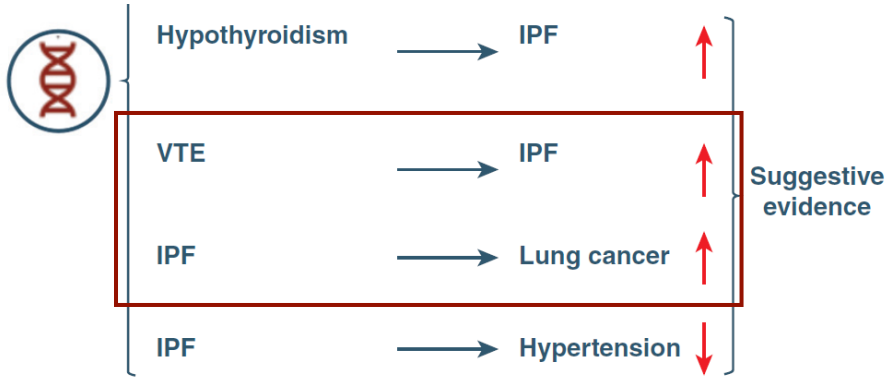
IPF → IPF-lung cancer

[Diffuse Lung Disease Original Research]

CHEST

A Causal Atlas on Comorbidities in Idiopathic Pulmonary Fibrosis: A Bidirectional Mendelian Randomization Study

Jiahao Zhu [1], Dan Zhou [2], Jing Wang [1], Ye Yang [1], Dingwan Chen [3], Fan He [4], Yingjun Li [5]



VTE: Venous thromboembolism

Causal association between IPF and comorbidities

Sources: Zhu, J., et al.,CHEST, 2023; Tzouvelekis, A., et al., CHEST, 2019.

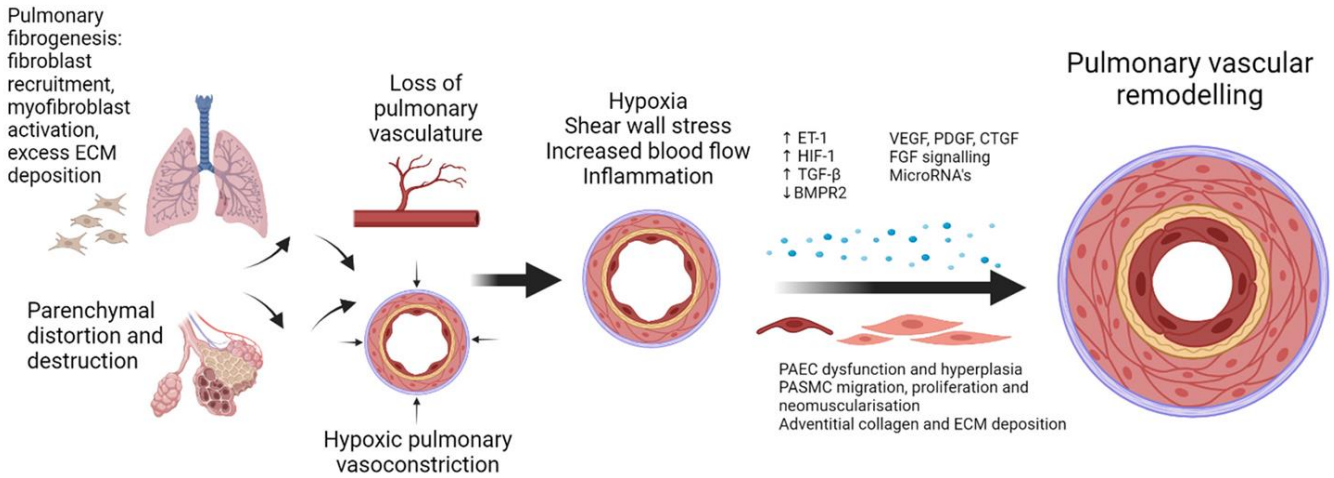
The pathophysiology of pulmonary hypertension in IPF

Review > Life (Basel). 2024 Sep 23;14(9):1203. doi: 10.3390/life14091203.

Converging Pathways: A Review of Pulmonary Hypertension in Interstitial Lung Disease

Alexandra Lawrence [1], Katherine Jane Myall [1 2], Bhashkar Mukherjee [1 3], Philip Marino [1]

The pathophysiology of pulmonary hypertension in interstitial lung disease



- **IPF is the most common interstitial lung disease (ILD)**
- **Pulmonary hypertension** (PH) in ILD is relatively common, **affecting up to 50% of patients with IPF**
- There is evidence for an **interplay between the disease pathogenesis** of fibrotic ILD and PH

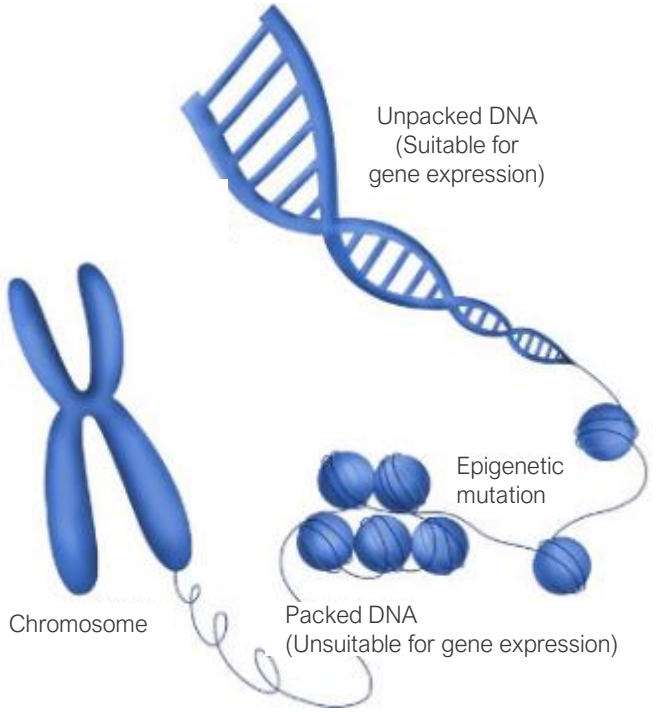
Source: Lawrence, A., et al., Life, 2024.

High unmet medical need for a new disease-modifying therapy

- **IPF** is a **devastating disease** with poor quality of life and **no cure**
- Similar survival rates as worst types of cancers
- Current pharmacological therapy has:
  - Poor tolerability
  - No effects on disease symptoms
  - Modest effect on disease progression
  - No effect on mortality
- **Need for safe and well-tolerated therapy** with both symptomatic relief as well as profound effect/stabilization of disease progression

Cereno's HDACi portfolio is untapping the potential of epigenetic modulation in CVD

- Histone deacetylase inhibition (HDACi) plays important role in epigenetic modulation.[1-14]
- Epigenetic modulation - alteration of gene expression without altering genetic material.[1,2]



Disease-modifying elements of CVD addressed by HDACi in particular VPA

1. Reverse pathological remodeling
2. Anti-fibrotic
3. Anti-inflammatory
4. Pulmonary pressure reduction
5. Anti-thrombotic (fibrinolytic, anti-platelet)

THE LANCET
Healthy Longevity
Histone deacetylase inhibitors for cardiovascular conditions and healthy longevity

Source:1. Ferreira JP, Pitt B, and Zannad F, Lancet Healthy Longev 2021;2,e371-379; 2. Bisserier M. et.al. Vasc Biol. 2020 Jan;2(1):R17-R34. 3. Duenas-Gonzales, A., et al, 2008, Link; 4. Han, W., et al, 2021, Link; 5. Kabel, A., et al, 2016, Link; 6. Lan, B., et al, 2015, Link; 7. Zhao, L., et al, 2012, Link; 8. Cardinale, J., et al, 2010, Link; 9. Costalonga, E., et al, 2017, Link; 10. Seet, L., et al, 2019, Link; 11. Wu, S., et al, 2015, Link; 12. Larsson, P., et al, 2016, Link; 13. Saluveer, O., et al, 2014, Link; 14. Svennerholm, K., et al, 2015, Link.

Potential of Cereno's pipeline of HDACi epigenetic modulators (CS1, CS014) based on unique efficacy profile*

Cardiovascular disease	Efficacy profile of HDACi epigenetic modulators	Systemic blood pressure reduction	Pulmonary pressure reduction	Anti-thrombotic	Anti-inflammatory/ Organ protection	Anti-fibrotic/ Reverse remodeling
PAH	CS1		✓	✓	✓	✓
VTE				✓	✓	✓
AF (SPAF)		✓		✓	✓	✓
Secondary prev. MI/Stroke		✓	✓	✓	✓	✓
HFpEF		✓	✓		✓	✓
HFrEF (post-MI)			✓	✓	✓	✓
Kidney failure		✓		✓	✓	✓
Cardiac transplantation				✓	✓	✓
Diabetes		✓		✓	✓	✓
IPF	CS014		✓	✓	✓	✓

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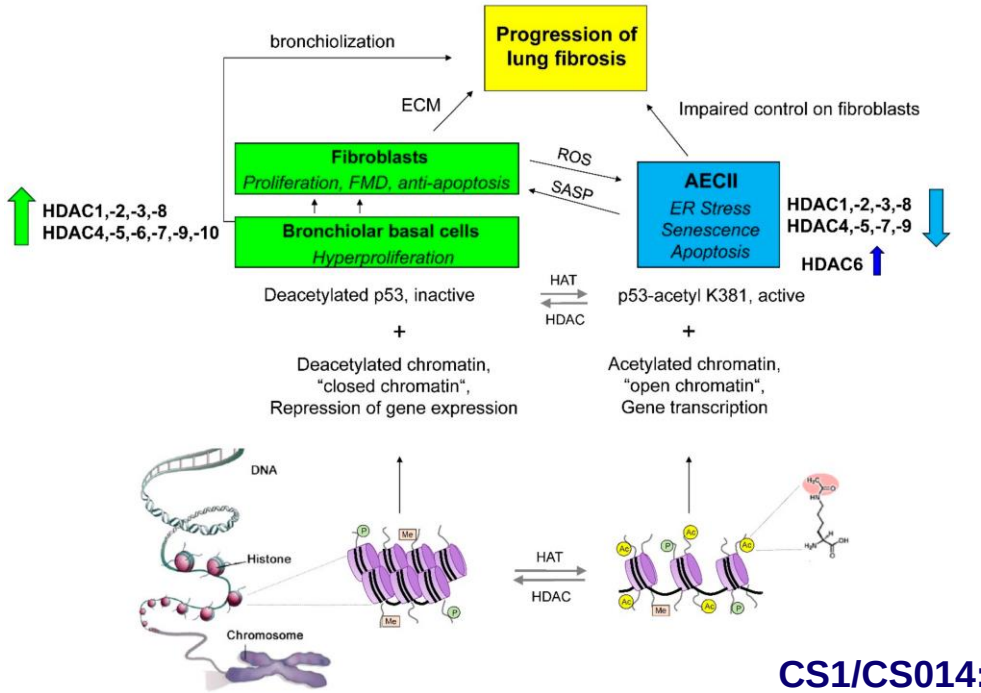
*Unique efficacy profile of VPA and HDAC inhibitors
EH: Essential Hypertension; AF: Atrial Fibrillation; SPAF: Stroke Prevention in Arterial Hypertension; HFpEF: Heart Failure with preserved Ejection Fraction; HFrEF: Heart Failure with reduced Ejection Fraction; Post-MI: Post Myocardial Infarction; IPF: Idiopathic Pulmonary Fibrosis

IPF is characterized by a significant imbalance of histone deacetylase (HDAC) activities

Review

Targeting Histone Deacetylases in Idiopathic Pulmonary Fibrosis: A Future Therapeutic Option

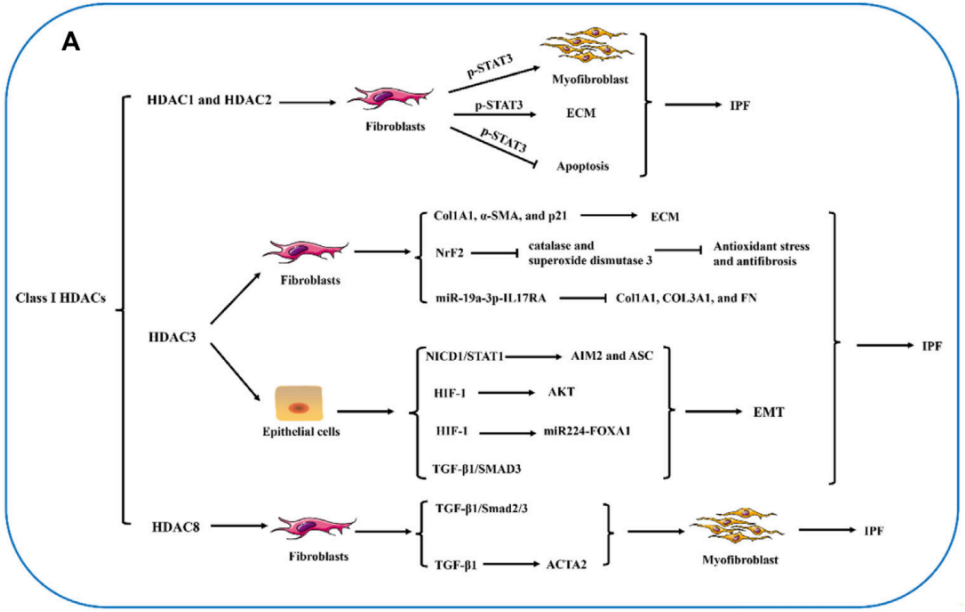
Martina Korfei [1,2,*], Poornima Mahavadi [1,2] and Andreas Guenther [1,2,3,4,†]



CS1/CS014: Class I HDACi

Histone deacetylases: potential therapeutic targets for idiopathic pulmonary fibrosis

Hai-peng Cheng[1,2], Shi-he Jiang[1,2], Jin Cai[1,2], Zi-qiang Luo[3,4], Xiao-hong Li[1,2]* and Dan-dan Feng[3]*



Sources: Korfei et al., Cells (2022); Cheng et al., Front. Cell Dev. Biol. (2024)

Direct correlation between PAI-1 expression and the extent of collagen accumulation that follows inflammatory lung injury

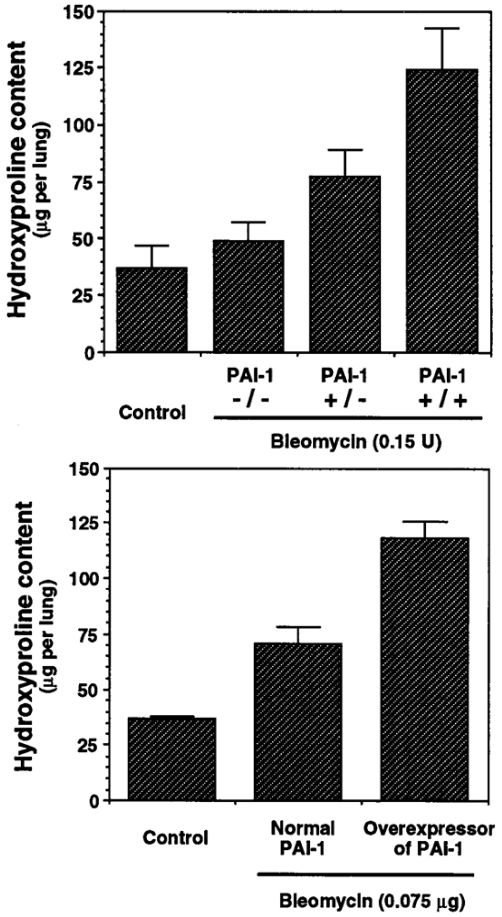
J Clin Invest. 1996 Jan 1; 97(1): 232–237.
doi: 10.1172/JCI118396

PMCID: PMC507084
PMID: 8550840

Bleomycin-induced pulmonary fibrosis in transgenic mice that either lack or overexpress the murine plasminogen activator inhibitor-1 gene.

D T Eitzman, R D McCoy, X Zheng, W P Fay, T Shen, D Ginsburg, and R H Simon

▸ Author information ▸ Copyright and License information PMC Disclaimer



- The data demonstrate a **direct correlation** between the genetically determined **level of PAI-1** expression and the extent of **collagen accumulation** that follows inflammatory lung injury
- The results strongly support the hypothesis that alterations in **fibrinolytic activity** influence the extent of **pulmonary fibrosis** that occurs after inflammatory injury

Hydroxyproline content is a proxy for collagen accumulation.

IPF patients have increased risk of venous thromboembolism

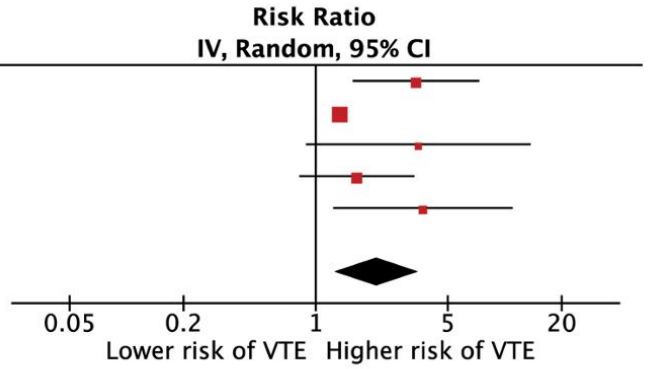
Sarcoidosis Vasc Diffuse Lung Dis. 2018; 35(2): 109–114.
Published online 2018 Aug 9. doi: 10.36141/svdld.v35i2.6213
PMCID: PMC7170087
PMID: 32476889

Risk of venous thromboembolism in patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis

Boonphiphop Boonpheng[1] and Patompong Ungprasert[2,3]

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Hubbard et al.	1.2208	0.3927	19.5%	3.39 [1.57, 7.32]	2008
Sprunger et al.	0.2927	0.0194	36.1%	1.34 [1.29, 1.39]	2012
Collard et al.	1.2499	0.6972	9.8%	3.49 [0.89, 13.69]	2012
Navaratnam et al.	0.5008	0.3568	21.2%	1.65 [0.82, 3.32]	2014
Dalleywater et al.	1.3056	0.5564	13.3%	3.69 [1.24, 10.98]	2014
Total (95% CI)			**100.0%**	**2.11 [1.28, 3.48]**	

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 11.06$, df = 4 (P = 0.03); $I^2 = 64\%$
Test for overall effect: Z = 2.92 (P = 0.003)



Meta-analysis:

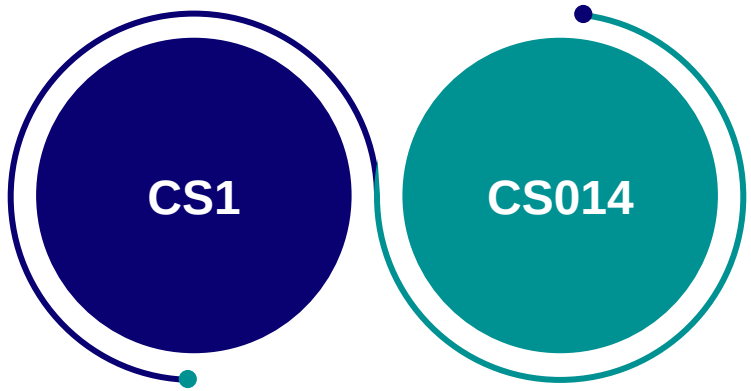
Several studies showing consistently the **increase in venous thromboembolism** in patients with **IPF**

Source: Boonpheng, B., Ungprasert, P., Sarcoidosis Vasc Diffuse Lung Dis., 2018.

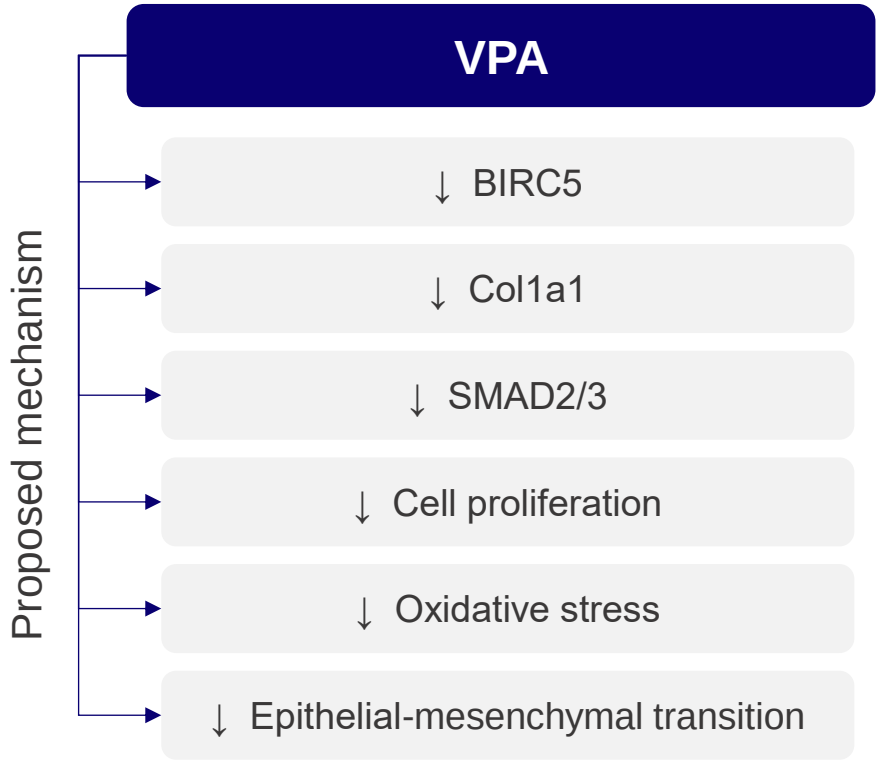
The development of CS014 aimed to retain the beneficial properties of valproate and improve its metabolism

CS1/CS014 correlation:

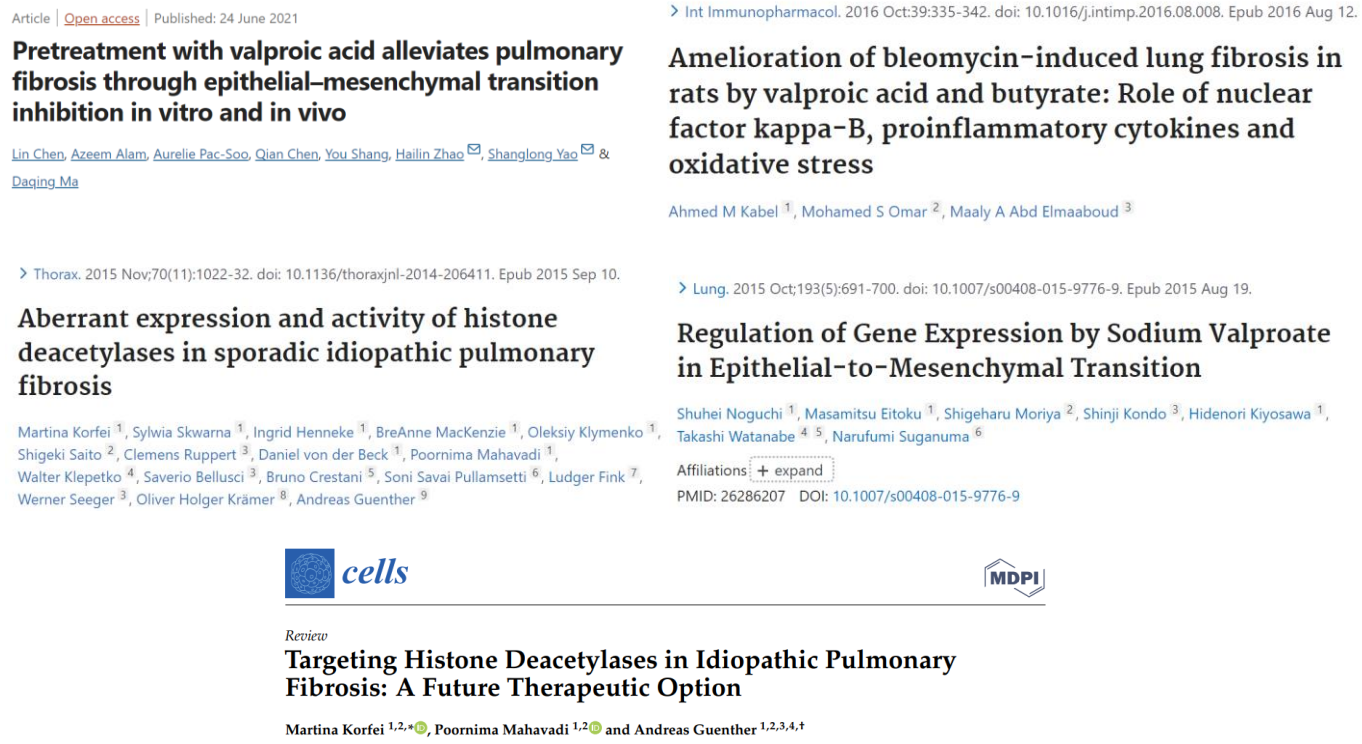
- CS014 is a **patent protected NCE that is close structural analog** of CS1
- Preclinical studies reveal **very similar primary pharmacology** (PK/PD) compared with VPA
- **Same exposures** of CS1 & CS014 induce similar **magnitude of effect**, e.g., HDAC inhibition potencies are equivalent



VPA alleviates fibrosis in IPF



Alleviation of lung fibrosis



Article | Open access | Published: 24 June 2021

Pretreatment with valproic acid alleviates pulmonary fibrosis through epithelial–mesenchymal transition inhibition in vitro and in vivo

Lin Chen, Azeem Alam, Aurelie Pac-Soo, Qian Chen, You Shang, Hailin Zhao, Shanglong Yao & Daqing Ma

› Int Immunopharmacol. 2016 Oct;39:335-342. doi: 10.1016/j.intimp.2016.08.008. Epub 2016 Aug 12.

Amelioration of bleomycin-induced lung fibrosis in rats by valproic acid and butyrate: Role of nuclear factor kappa-B, proinflammatory cytokines and oxidative stress

Ahmed M Kabel [1], Mohamed S Omar [2], Maaly A Abd Elmaaboud [3]

› Thorax. 2015 Nov;70(11):1022-32. doi: 10.1136/thoraxjnl-2014-206411. Epub 2015 Sep 10.

Aberrant expression and activity of histone deacetylases in sporadic idiopathic pulmonary fibrosis

Martina Korfei [1], Sylwia Skwarna [1], Ingrid Henneke [1], BreAnne MacKenzie [1], Oleksiy Klymenko [1], Shigeki Saito [2], Clemens Ruppert [3], Daniel von der Beck [1], Poornima Mahavadi [1], Walter Klepetko [4], Saverio Bellusci [3], Bruno Crestani [5], Soni Savai Pullamsetti [6], Ludger Fink [7], Werner Seeger [3], Oliver Holger Krämer [8], Andreas Guenther [9]

› Lung. 2015 Oct;193(5):691-700. doi: 10.1007/s00408-015-9776-9. Epub 2015 Aug 19.

Regulation of Gene Expression by Sodium Valproate in Epithelial-to-Mesenchymal Transition

Shuhei Noguchi [1], Masamitsu Eitoku [1], Shigeharu Moriya [2], Shinji Kondo [3], Hidenori Kiyosawa [1], Takashi Watanabe [4 5], Narufumi Suganuma [6]

Affiliations + expand

PMID: 26286207 DOI: 10.1007/s00408-015-9776-9

cells MDPI

Review

Targeting Histone Deacetylases in Idiopathic Pulmonary Fibrosis: A Future Therapeutic Option

Martina Korfei [1,2,*], Poornima Mahavadi [1,2] and Andreas Guenther [1,2,3,4,†]

- **BIRC5** is an immune-related gene that inhibits apoptosis and promotes cell proliferation
- **Col1a1** gene encodes the alpha-1 subunit of the fibril-forming type I collagen
- **SMAD2/3** are proteins that mediate the signal of the transforming growth factor (TGF)-beta

Cereno Scientific

Source: Chen, L., et al., Lab Invest, 2021; Kabel, A., et al. Intern Immunopharmacology, 2016; Noguchi, S., et al., Lung, 2015; Korfei, M., et al., Thorax, 2015; Korfei, M., et al., Cells, 2022.

Preclinical data – Reduced fibrosis and multiple other important pulmonary arteriolar changes with CS014

Effect of 3-weeks CS014 oral dosing (20-300 mg/kg/day) on pulmonary arteriolar histopathology in the Sugen/hypoxia model:

- **Significantly reduced incidence of fibrosis** and fibroelastosis in the intima of arterioles
- Significant dose-dependent **reduction of:**
  - **Occlusion** of lung arterioles
  - Endothelial cell **proliferation**
  - Occurrence of **plexiform lesions**

Data in file.

Preclinical data – Regulation of platelet activity, local fibrinolysis, and clot stability with CS014

Cremaster arteriole laser-induced injury model:

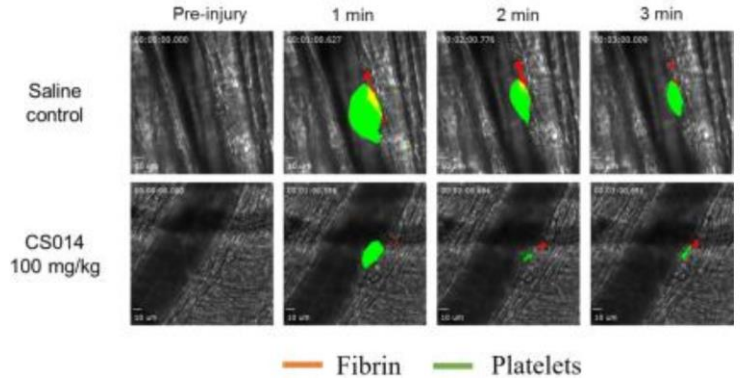
- CS014 treatment significantly reduced clot formation and fibrin formation at the site of injury

FeCl3-induced injury of the carotid artery assay:

- Treatment with CS014 was able to prevent full occlusion of the carotid artery

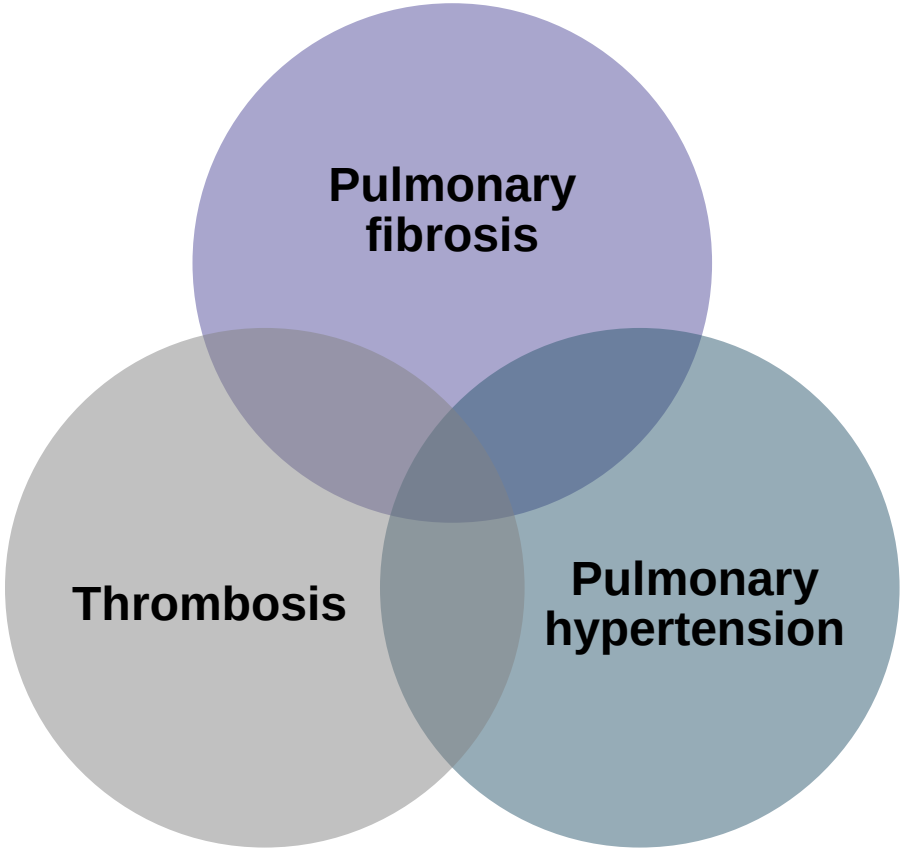
Saphenous vein rebleeding assay:

- Fibrin and platelet accumulation at the site of injury wound was significantly inhibited by CS014



Source: Holinstat, M., et al., European Heart Journal, 2022; Holinstat, M., et al., European Heart Journal, 2023.

IPF is closely related to pulmonary hypertension and thrombosis



- **IPF** patients have an increased risk of **venous thromboembolism**
- **Pulmonary hypertension** affects up to **50% of patients with IPF**
- **The pathogenic mechanisms of the diseases are correlated**

Leveraging a strong scientific rationale in a disease with high unmet medical need

Idiopathic Pulmonary Fibrosis:

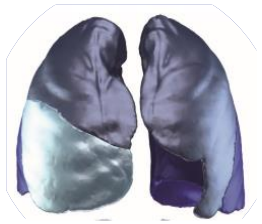
- **Devastating disease** with poor prognosis on par with worst cancers
- **Limited therapeutic options**; modest effect disease progression, dose-limiting toxicity and poor tolerability
- **High unmet need** for safe, well-tolerated disease-modifying therapy
- **Attractive market size**

CS014 scientific rationale in IPF:

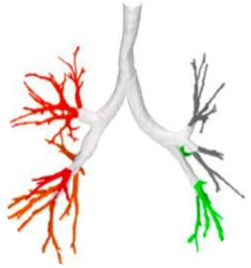
- **HDACi, in particular VPA,** has documented effects on **fibrosis, VTE and proliferation**
- **CS014** preclinical data has shown:
  - **Reversal of fibrosis and** a **dose-dependent** beneficial **effect on pathological vascular remodeling**
  - Regulation of platelet activity, local fibrinolysis, and clot stability
- Majority of IPF patients develop **pulmonary hypertension**
- Patients with IPF have **increased risk of VTE**

FRI PROVIDES COMPREHENSIVE SET OF QUANTITATIVE OUTCOME PARAMETERS

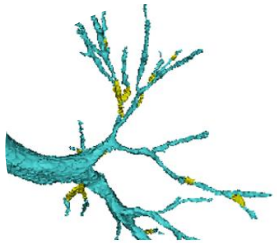
FLUIDDA



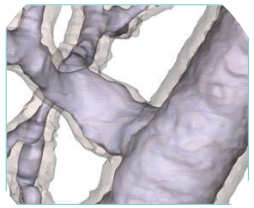
Lung Volumes



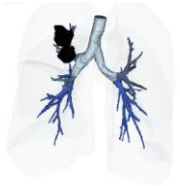
Airway Volumes



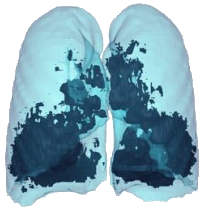
Mucus plugs



Airway Wall Thickness



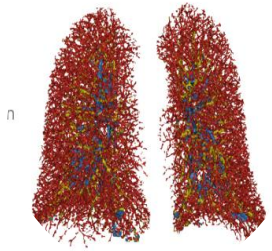
Nodules



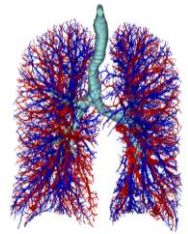
Emphysema

Air Trapping

Fibrosis

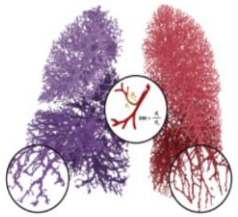


Blood Volume Distribution

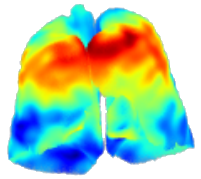


Arteries Veins

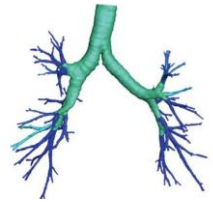
Blood Vessel Wall Thickness



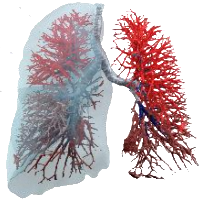
Vessel Tortuosity



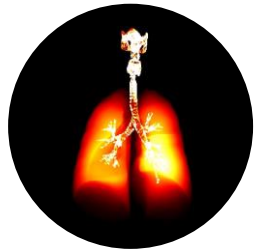
Ventilation



Airway Resistance



Ventilation/ Perfusion



Aerosol Deposition

LUNG & AIRWAY STRUCTURE

PARENCHYMAL STRUCTURE

BLOOD VESSELS STRUCTURE

PULMONARY FUNCTION

Agenda

Time	Discussion Item	Speaker
14:45	**Next steps for CS1**	**Dr. Rahul Agrawal** *CMO and Head of R&D, Cereno Scientific*
14:55	**Introduction to Fluidda and the innovative Functional Respiratory Imaging technology**	**Jan De Backer** *CEO Fluidda*
15:05	**Short break**	
15:15	**CS014 targeting unmet needs in rare disease IPF**	**Dr. Björn Dahlöf**, *CSO, Cereno Scientific*
15:35	**CS585 being evaluated rare diseases**	**Dr. Michael Holinstat** *Prof. at University of Michigan Medical School; and Director Translation Research, Cereno Scientific*
15:55	**Cereno Scientific - strategic priorities and future outlook**	**Sten R. Sörensen** *CEO, Cereno Scientific*
16:10	**Questions from Audience on site and online**	Moderated by Dr. Rahul Agrawal, *CMO and Head of R&D, Cereno Scientific*
16:25	**Concluding remarks**	**Sten R. Sörensen** *CEO, Cereno Scientific*

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

CS585 being evaluated in rare diseases

Cereno Scientific

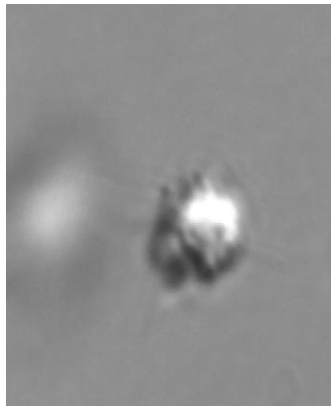
Cereno's portfolio is uniquely positioned to make impact in diseases with high unmet medical needs

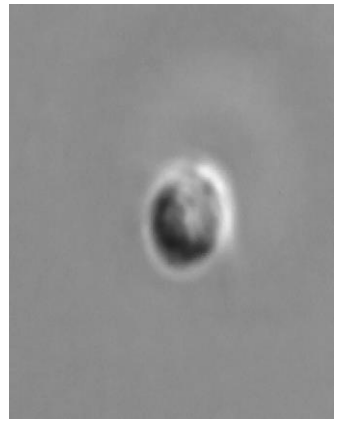
Program	Target	Indication	Preclinical	Phase I	Phase II	Phase III	Status
CS1	HDACi with disease-modifying potential	PAH					Phase II top-line results in Q3 2024[1] Expanded Access Program initiated in Q1 2024[1]
CS014	HDACi with disease-modifying potential	IPF					Phase I initiated in Q2 2024[2]
CS585	PRA oral, selective and potent	CVD					Ongoing preclinical development during 2024/25

Note: Progress bars are only an estimation, not to scale.

Source: 1. Cereno Press Release, 21st Feb 2024; 2. Cereno Press Release, 18th June 2024

Development of CS585 for regulation of platelet activation and thrombosis





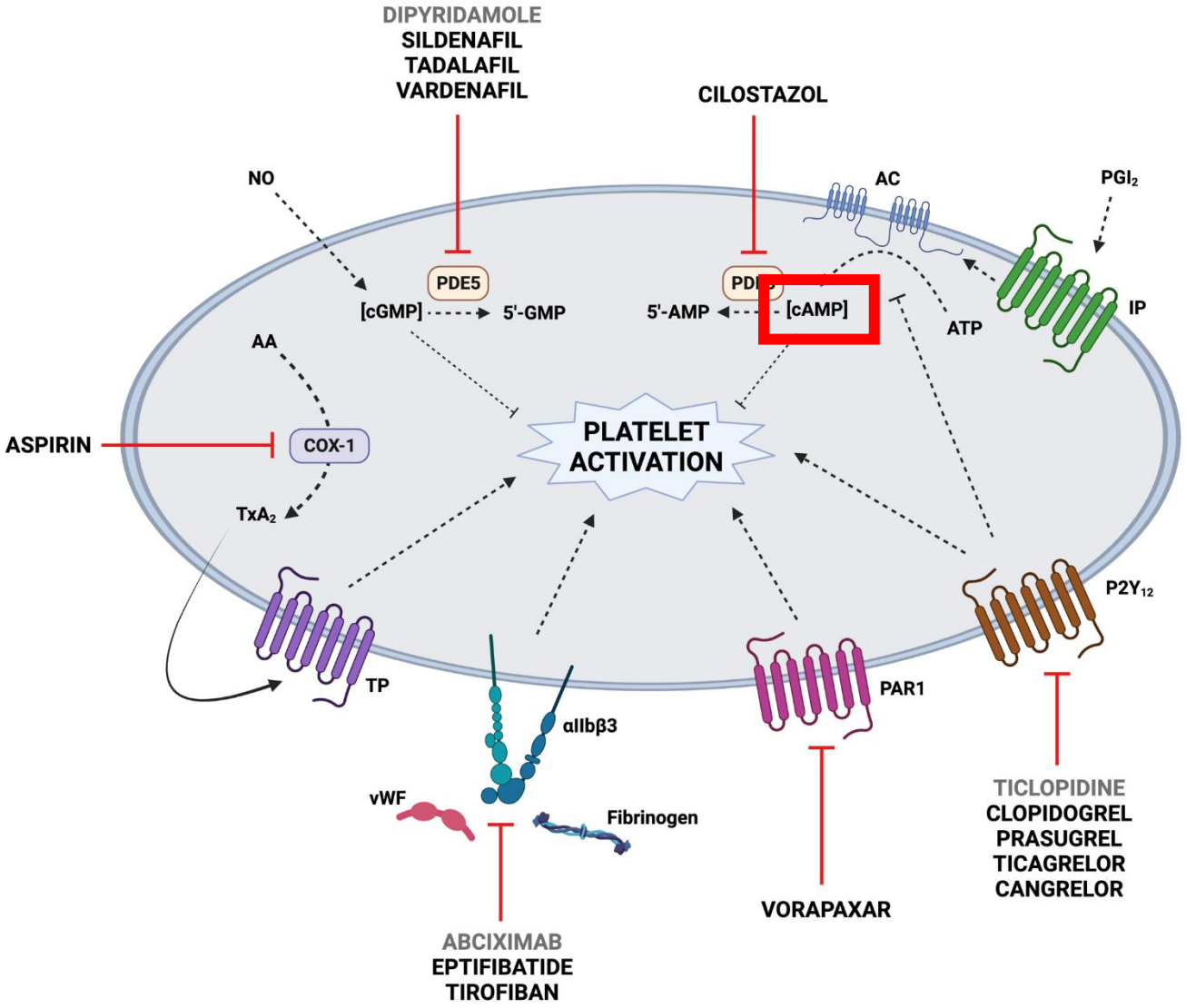
Michael Holinstat, PhD, FAHA

Professor, Departments of Pharmacology, Internal Medicine (division of cardiovascular medicine), and Vascular Surgery, University of Michigan

Director, Translational Research, Cereno Scientific

Cereno Scientific Capital Markets Day, Stockholm, Sweden
October 17th, 2024

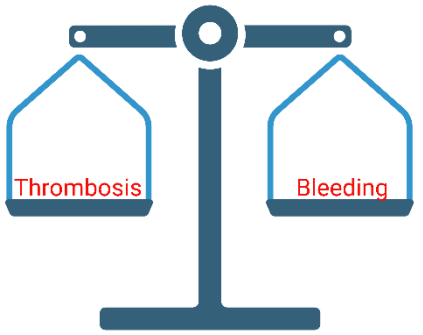
Regulation of human platelet function



- Antiplatelet therapies have reduced the risk of morbidity and mortality by more than 26%
- However, morbidity and mortality due to cardiovascular events remain a significant problem

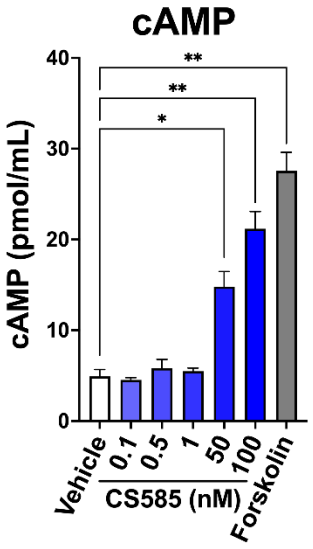
Novel antiplatelet therapies must:

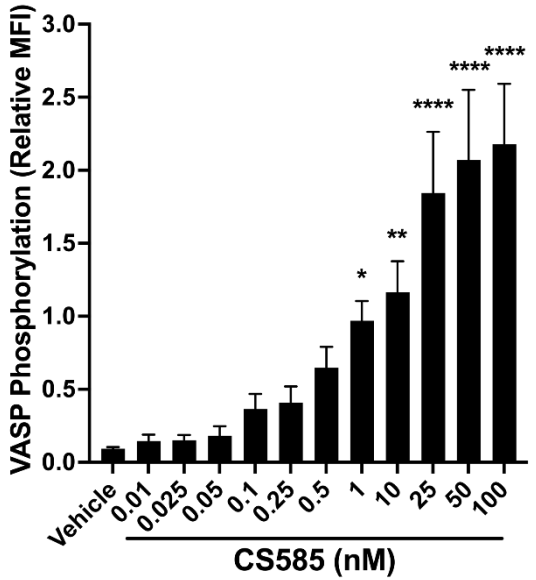
- **Decrease platelet activation and thrombosis**
- **Limit risk of bleeding and intracranial hemorrhage**

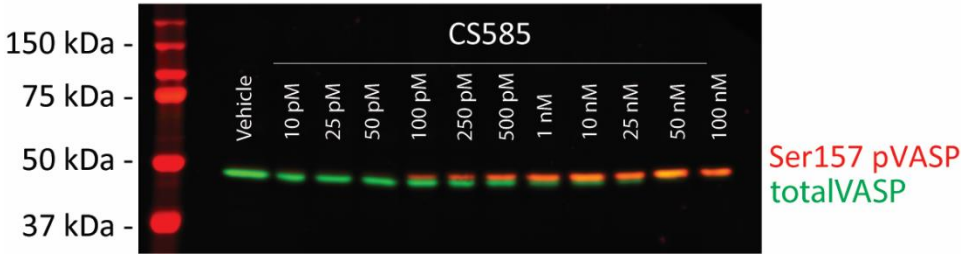


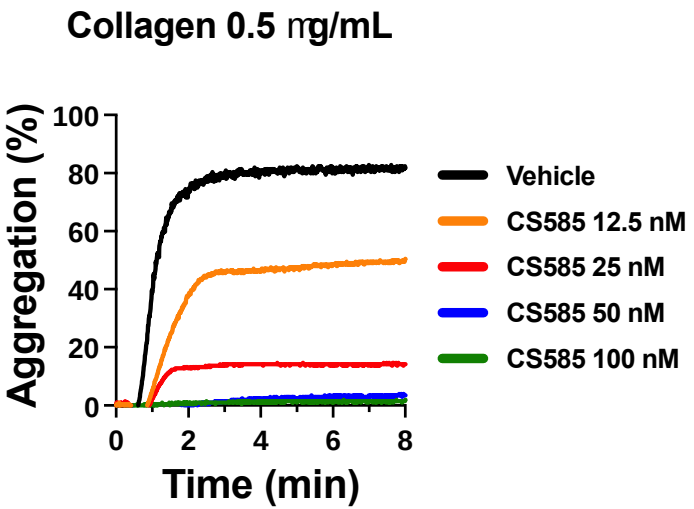
Stanger et al, Journal of Thrombosis & Haemostasis. 2023.

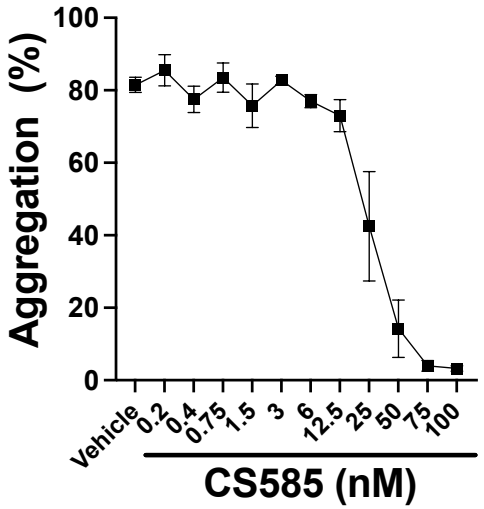
CS585 decreases platelet activity through activation of the IP receptor

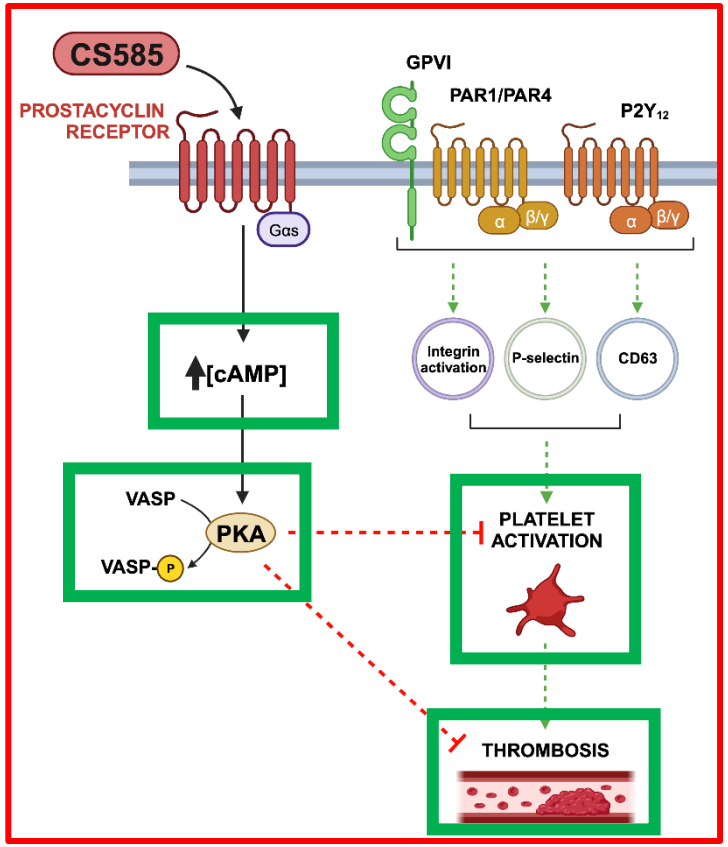


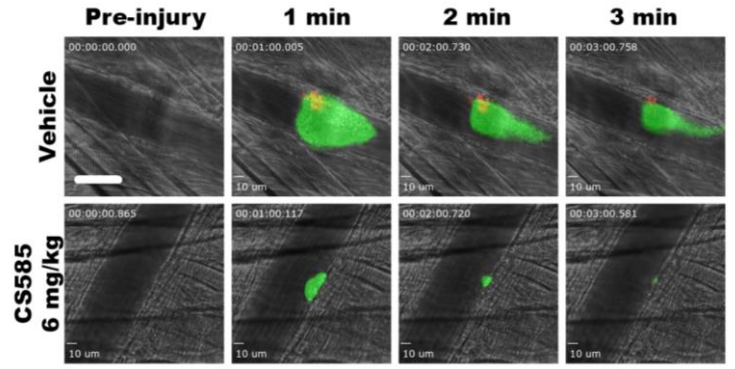












Scale bar = 50 µm

Stanger et al, Blood. 2023.

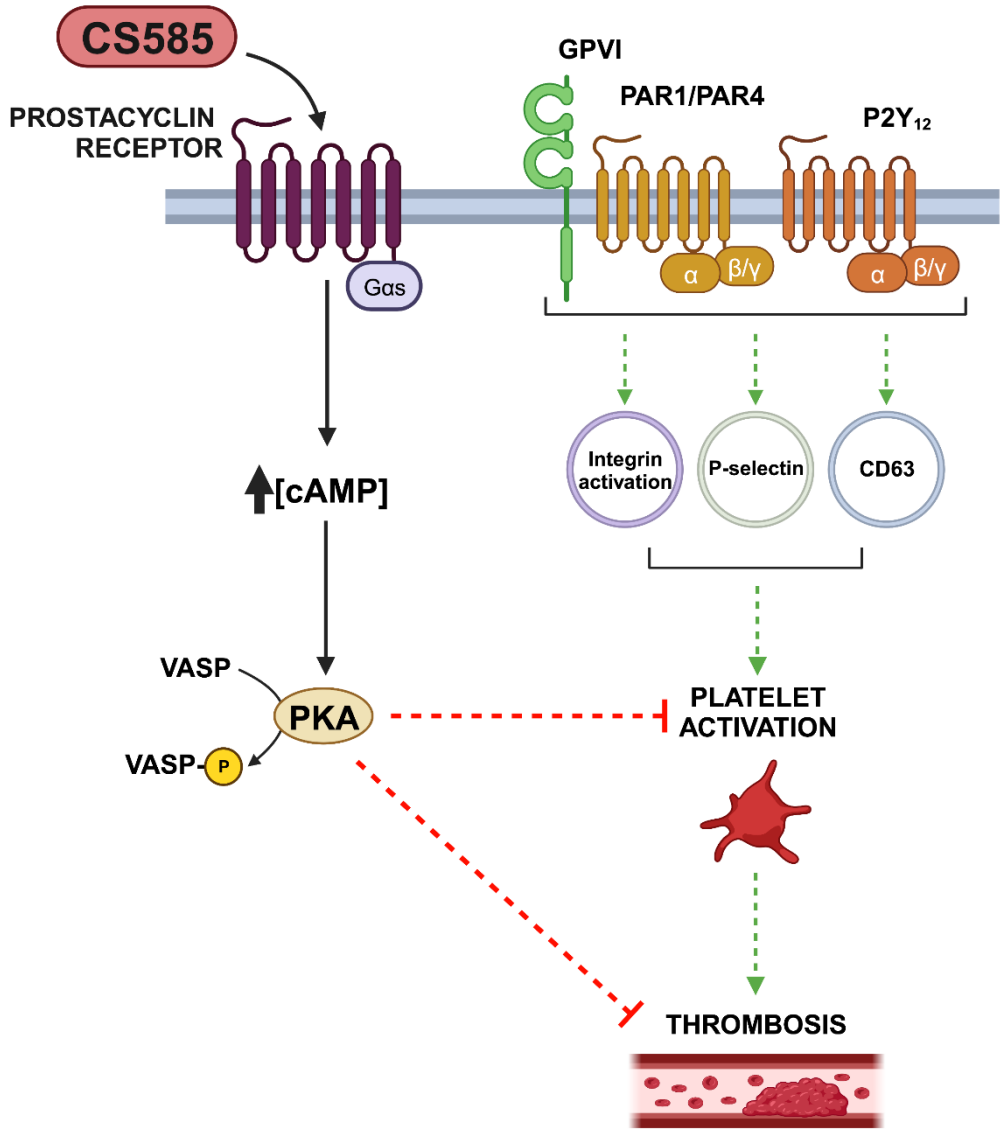
IP receptor agonist selectivity

- Previously developed IP receptor agonists lack selectivity for the IP receptor

➢ Is CS585 more selective compared to other IP receptor agonists?

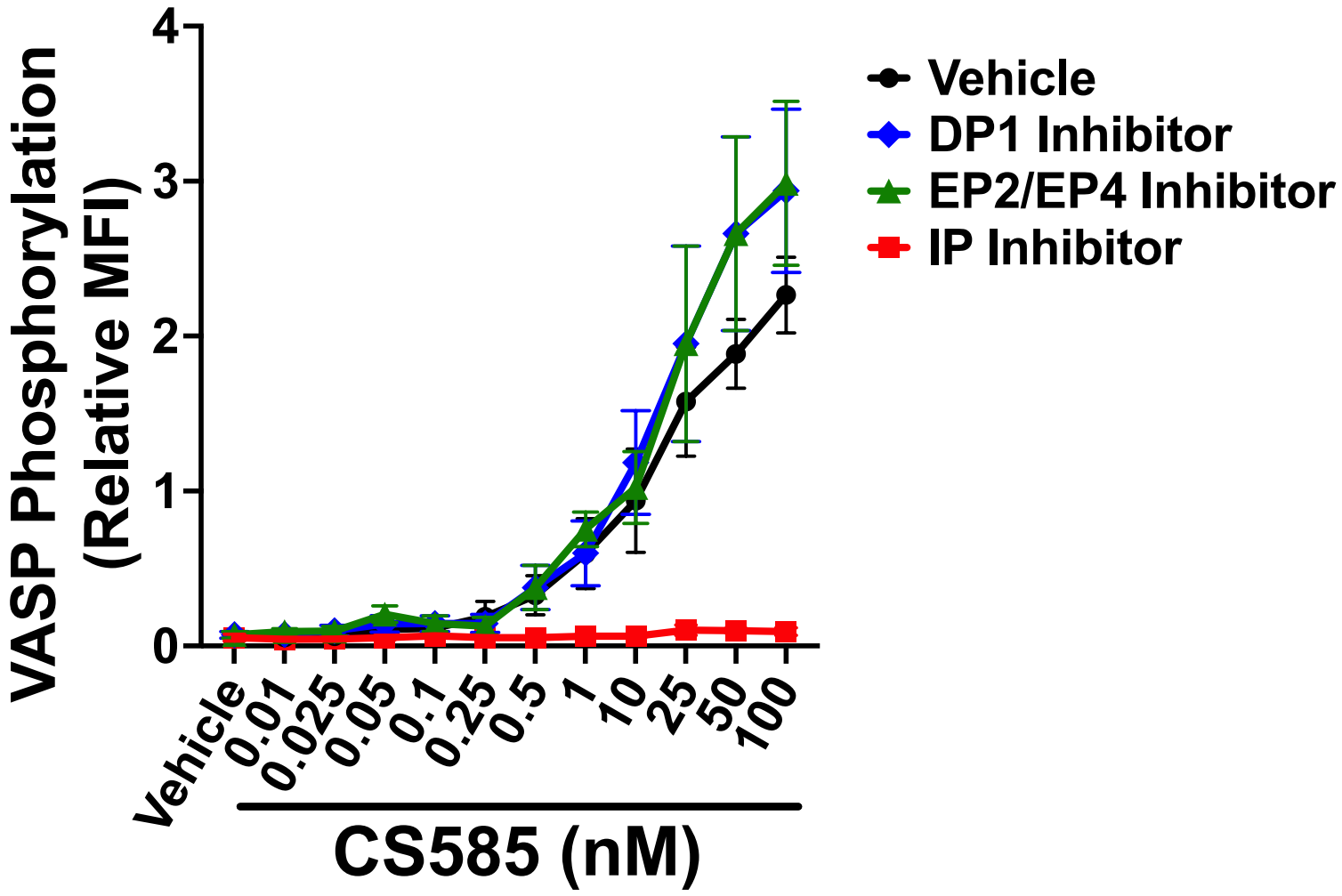
➢ Does CS585 exhibit long-lasting inhibition of platelet activity and clotting

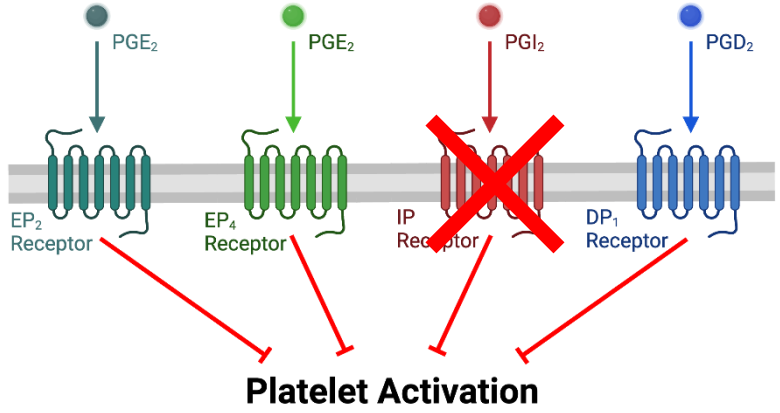
CS585 selectively targets the IP receptor to inhibit platelet activation and thrombosis

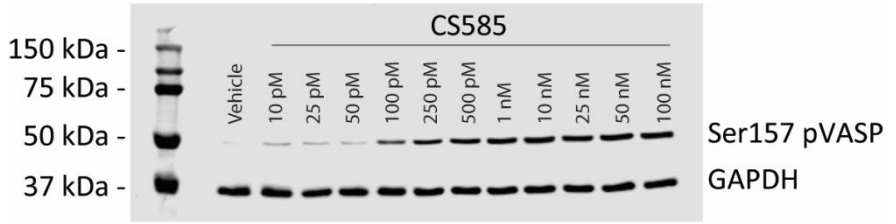


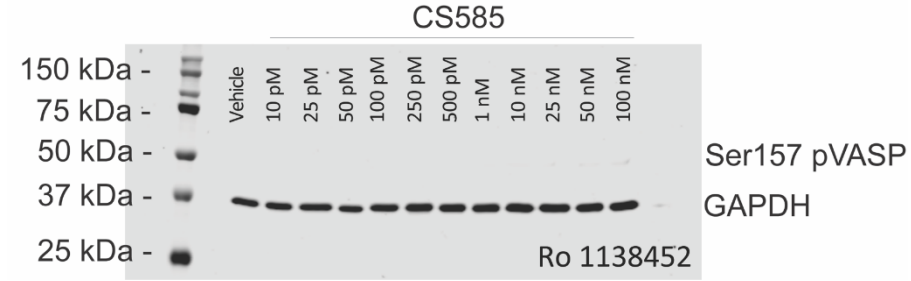
Stanger et al, Blood. 2023.

CS585 selectively signals though activation of the prostacyclin receptor





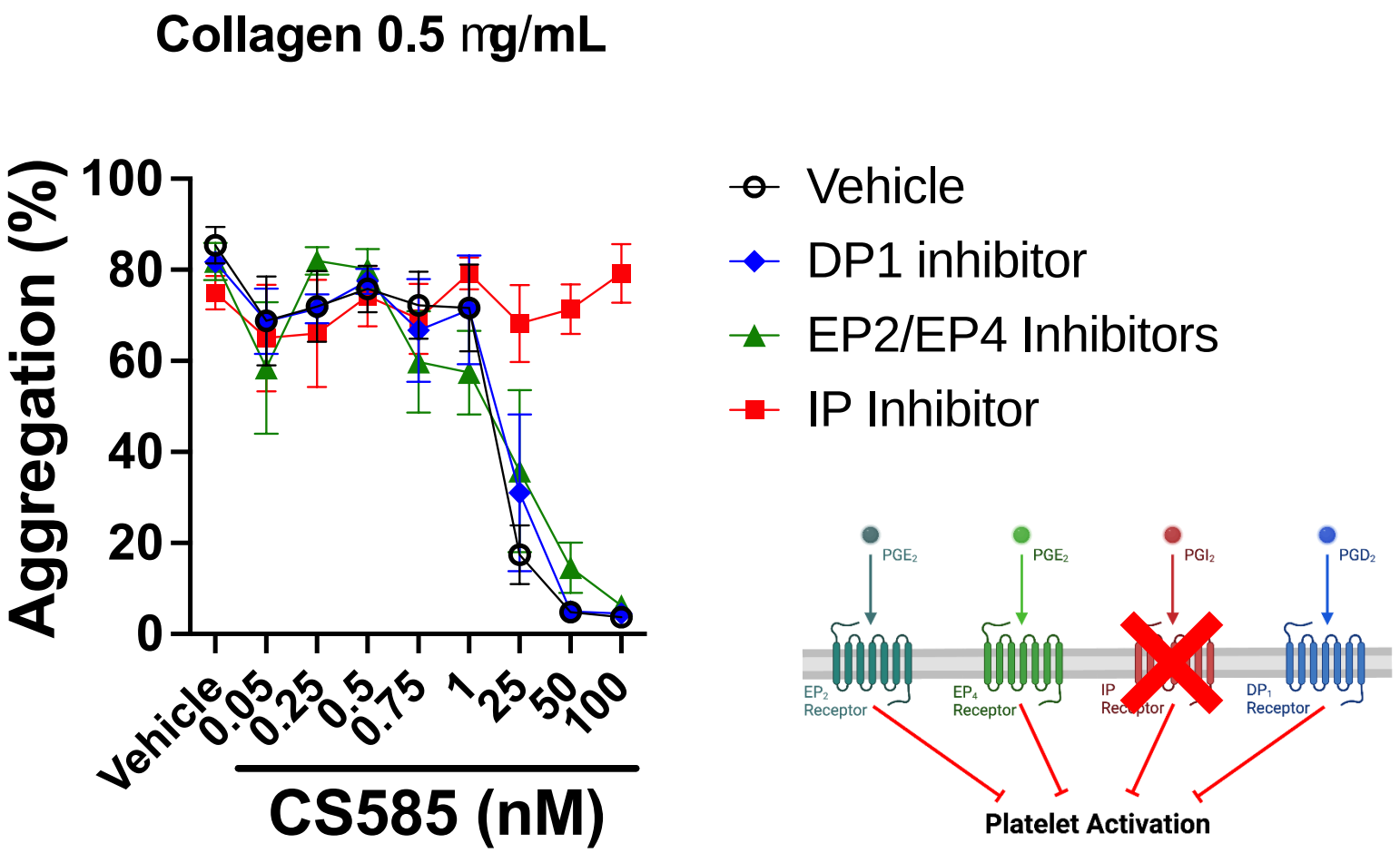


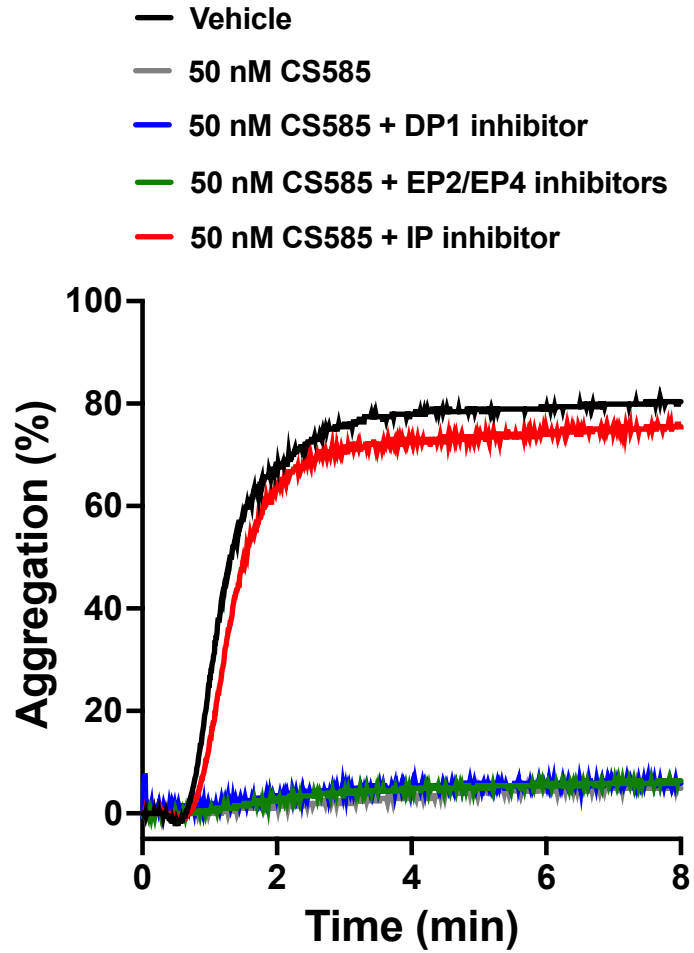


IP Inhibitor: Ro 1138452

Stanger et al, Blood. 2023.

CS585 inhibits platelet aggregation selectively through the prostacyclin receptor



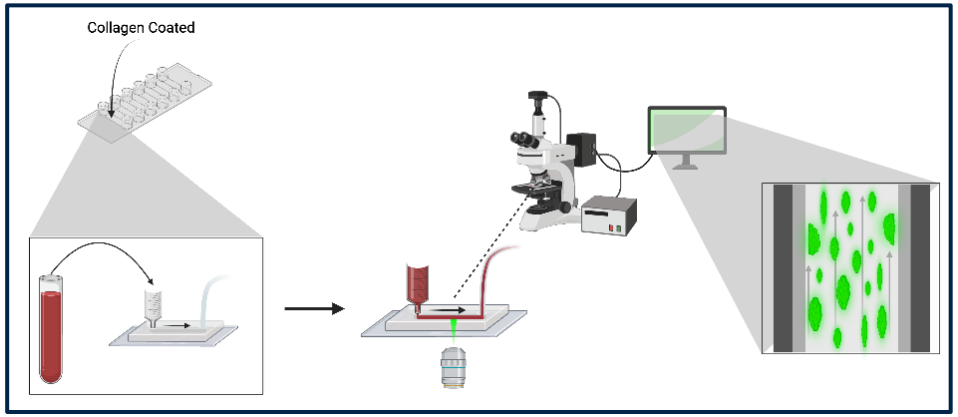


IP Inhibitor: Ro 1138452

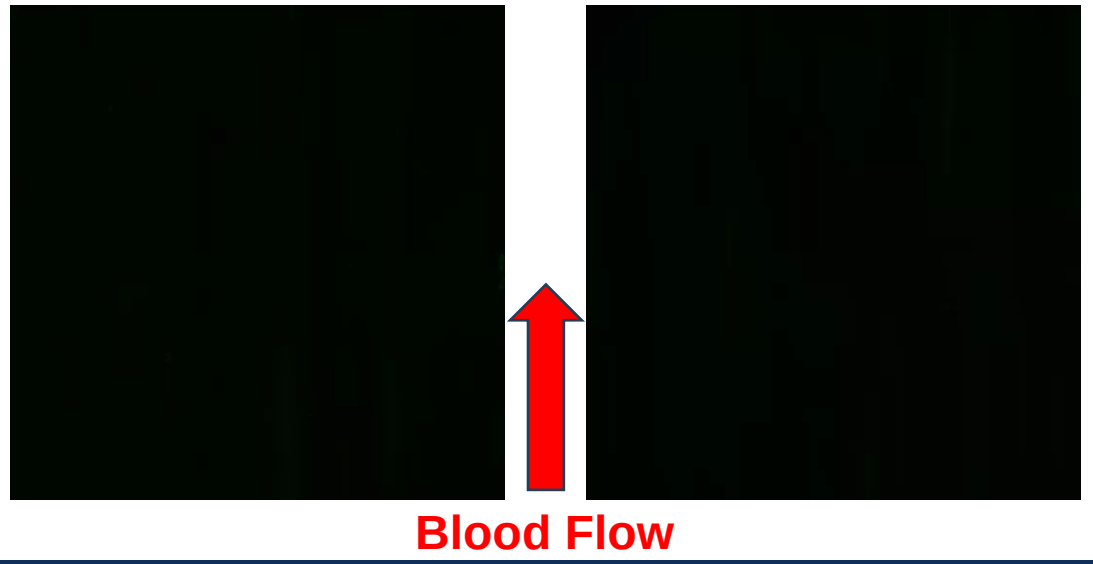
Stanger et al, Blood. 2023.

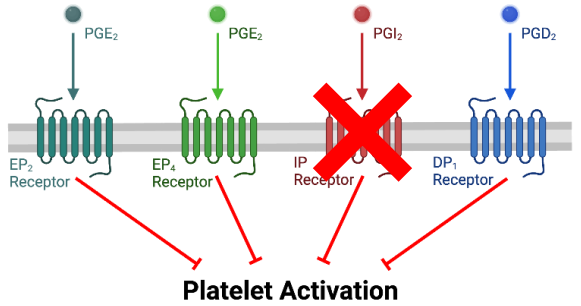
CS585 is selective for the IP receptor in whole blood

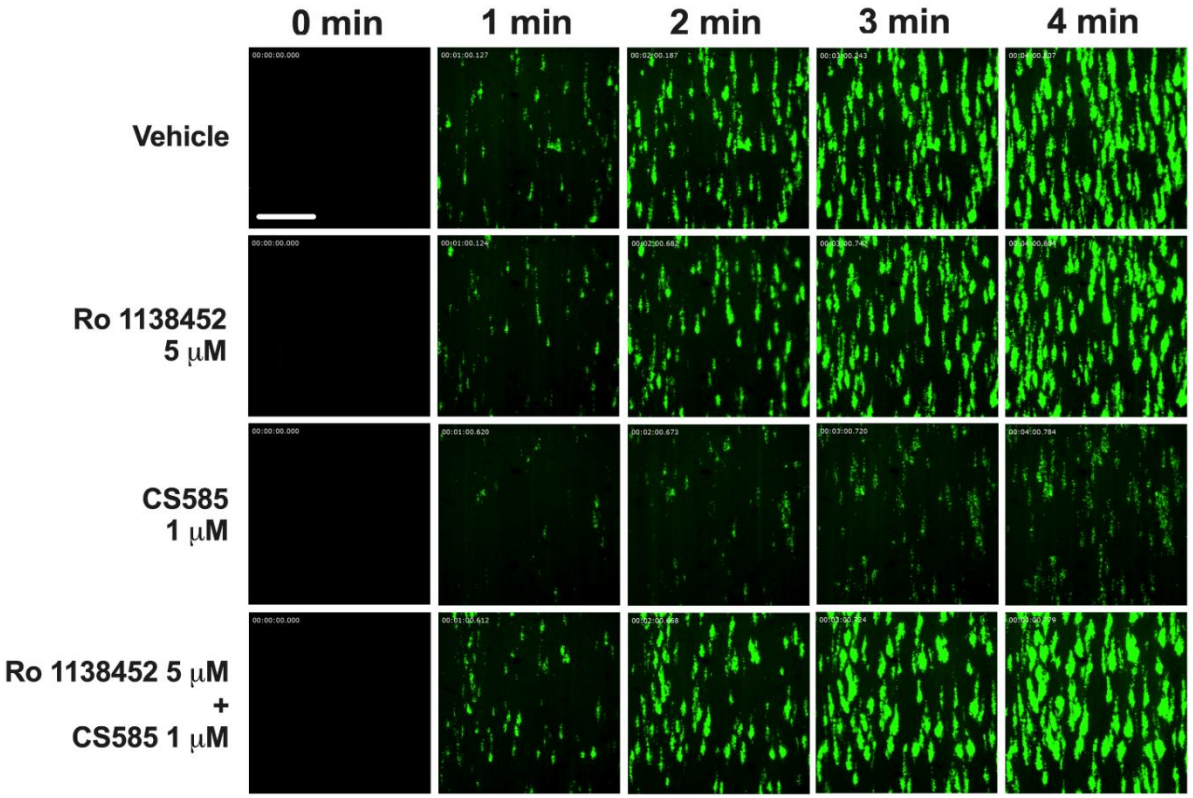
Perfusion Flow Chamber



Vehicle **CS585**



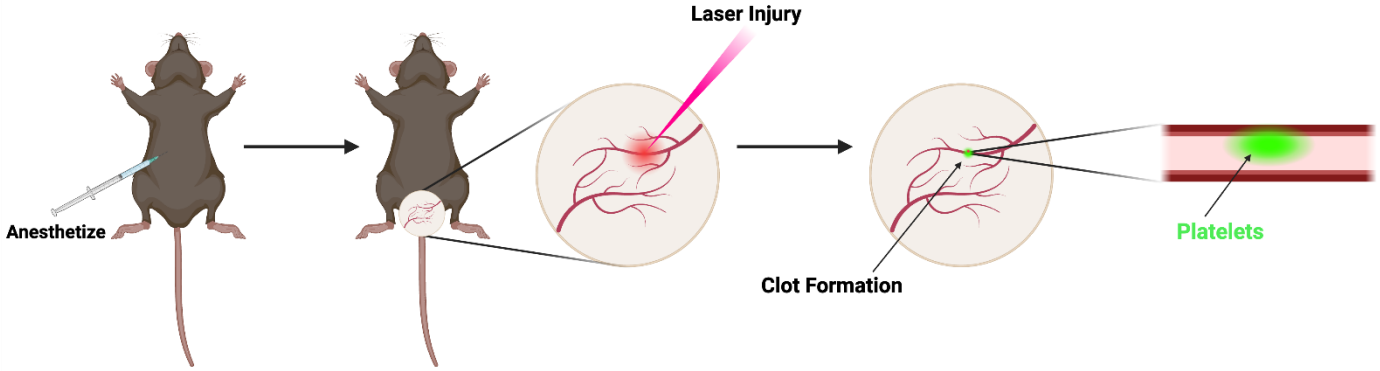


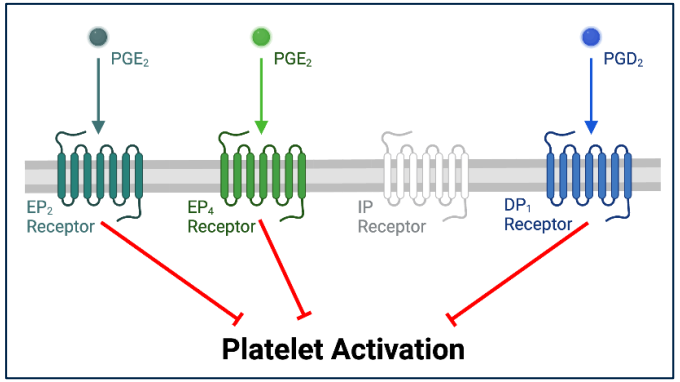


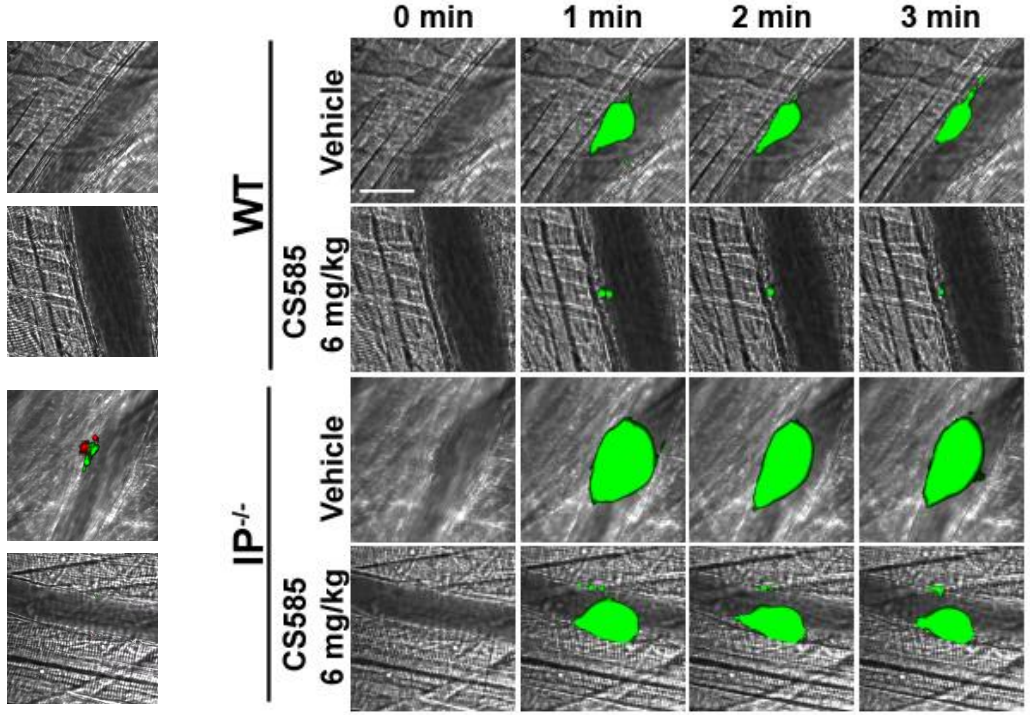
IP Inhibitor: Ro 1138452

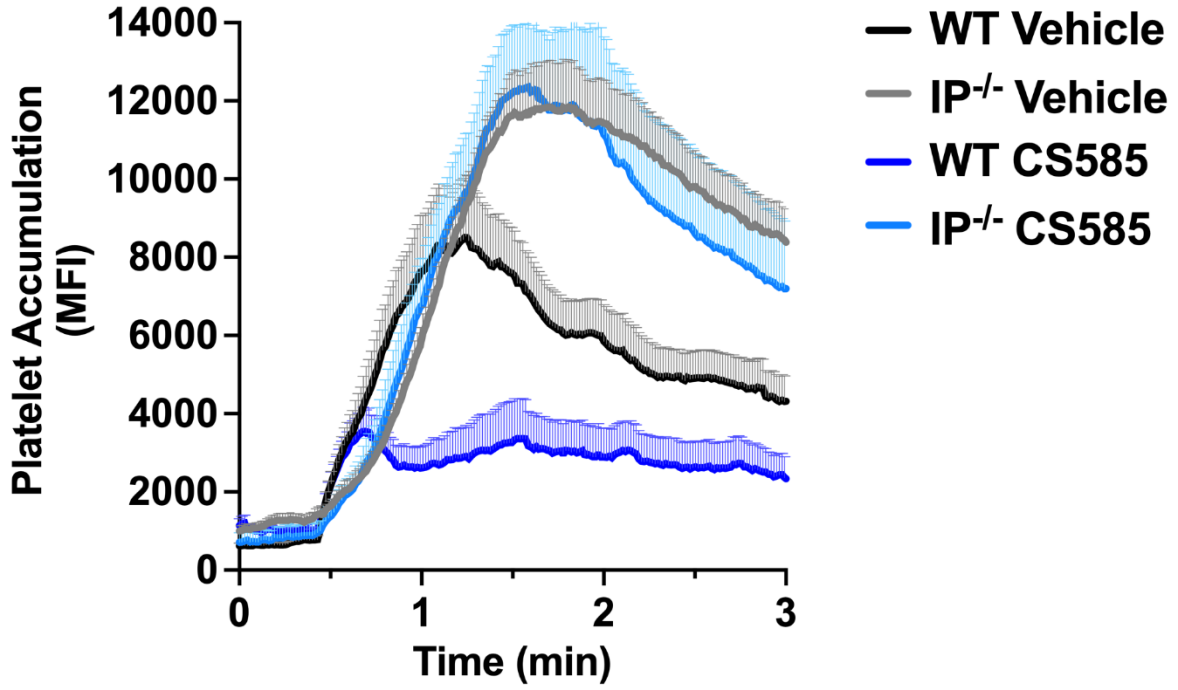
Stanger et al, Blood. 2023.

Is CS585 selective for the IP receptor *in vivo*?





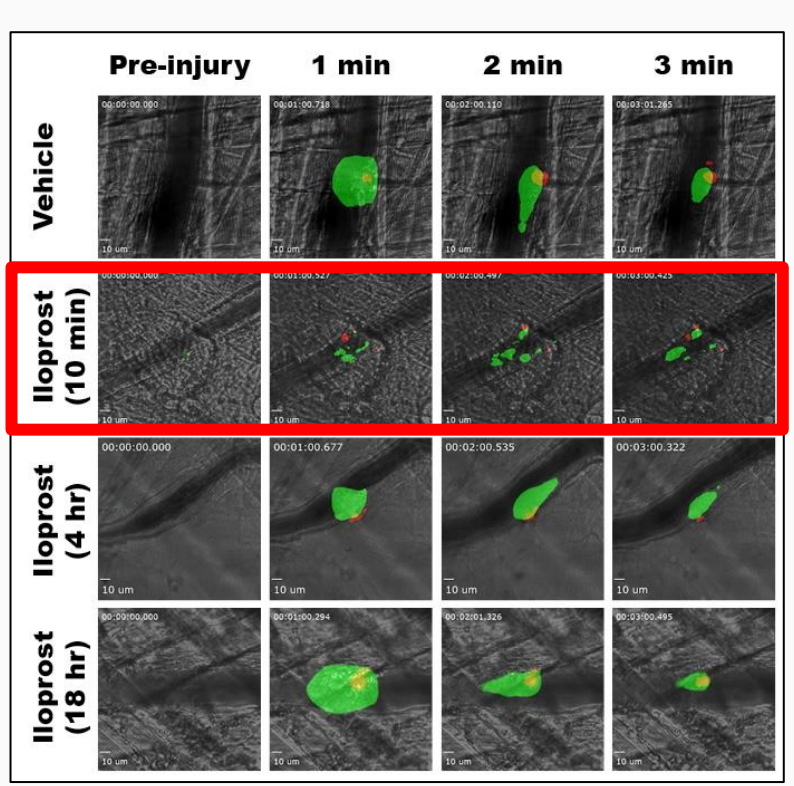


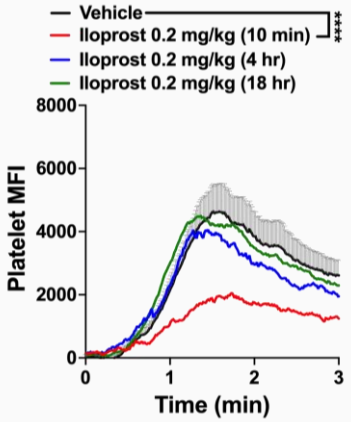


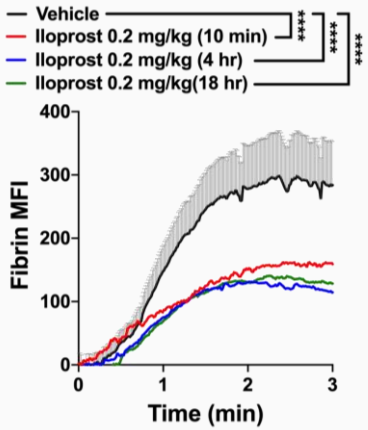
Unpublished.

Current IP agonists decrease platelet accumulation for up to 4 hours following IV administration

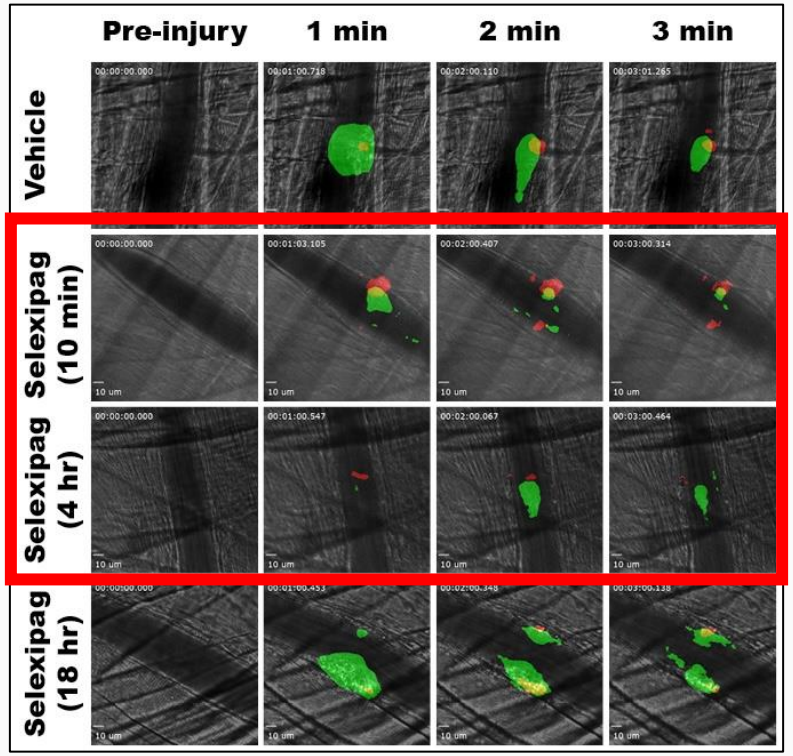
Iloprost

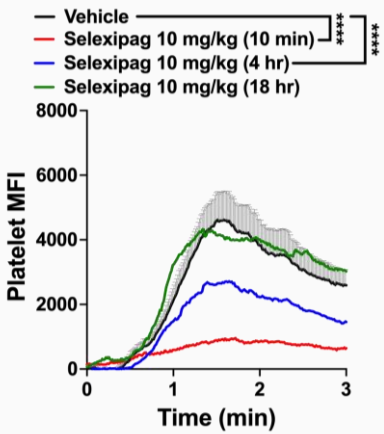


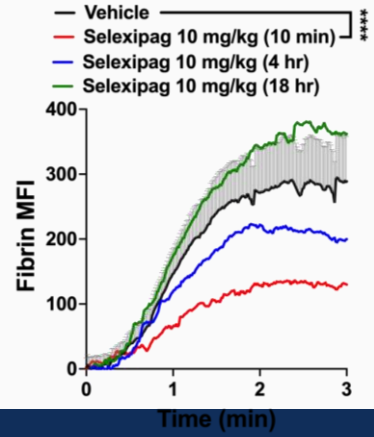




Selexipag

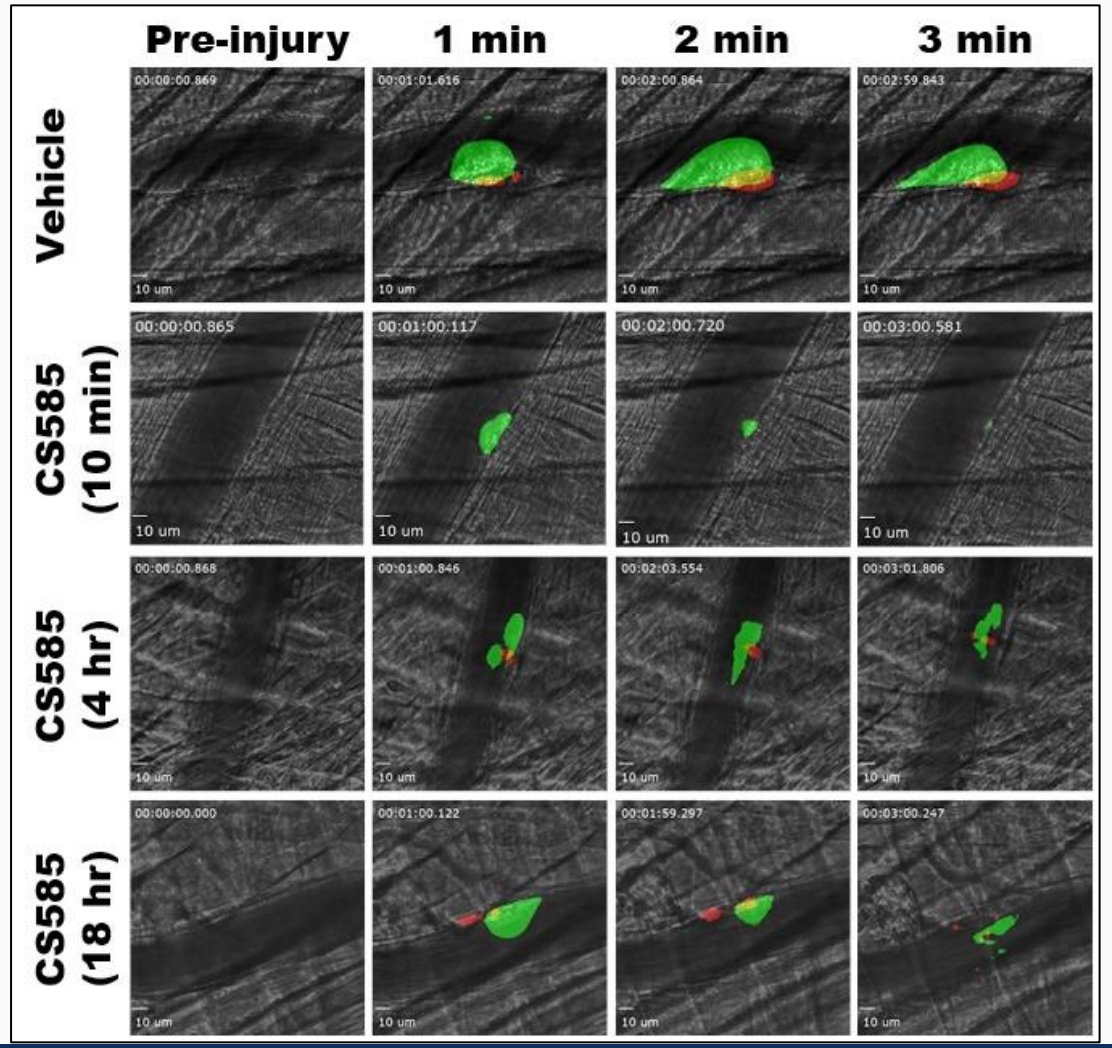


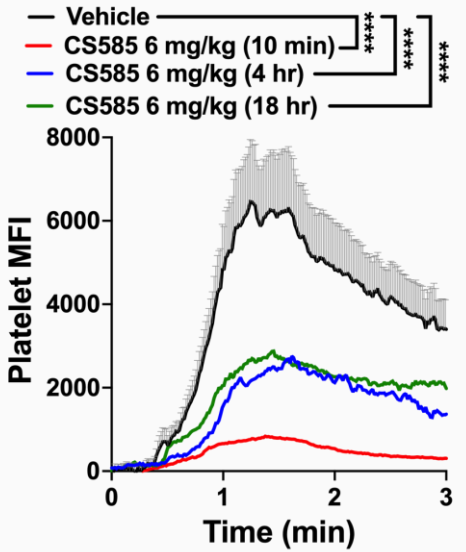


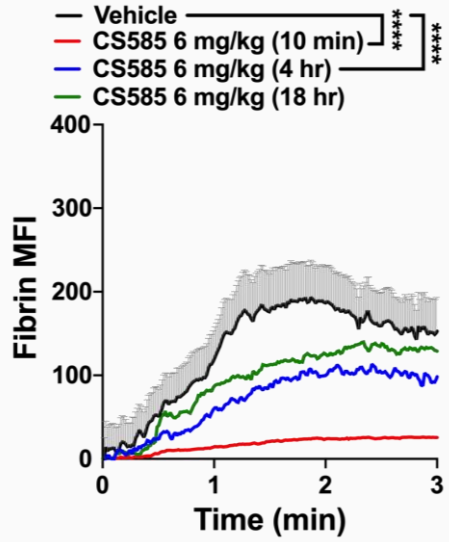


CS585 exhibits long-lasting inhibition of thrombus formation following IV administration

- Single IV administration
- Inhibition of 6 mg/kg CS585:
  - Platelet activation
  - Platelet adhesion
  - Fibrin formation



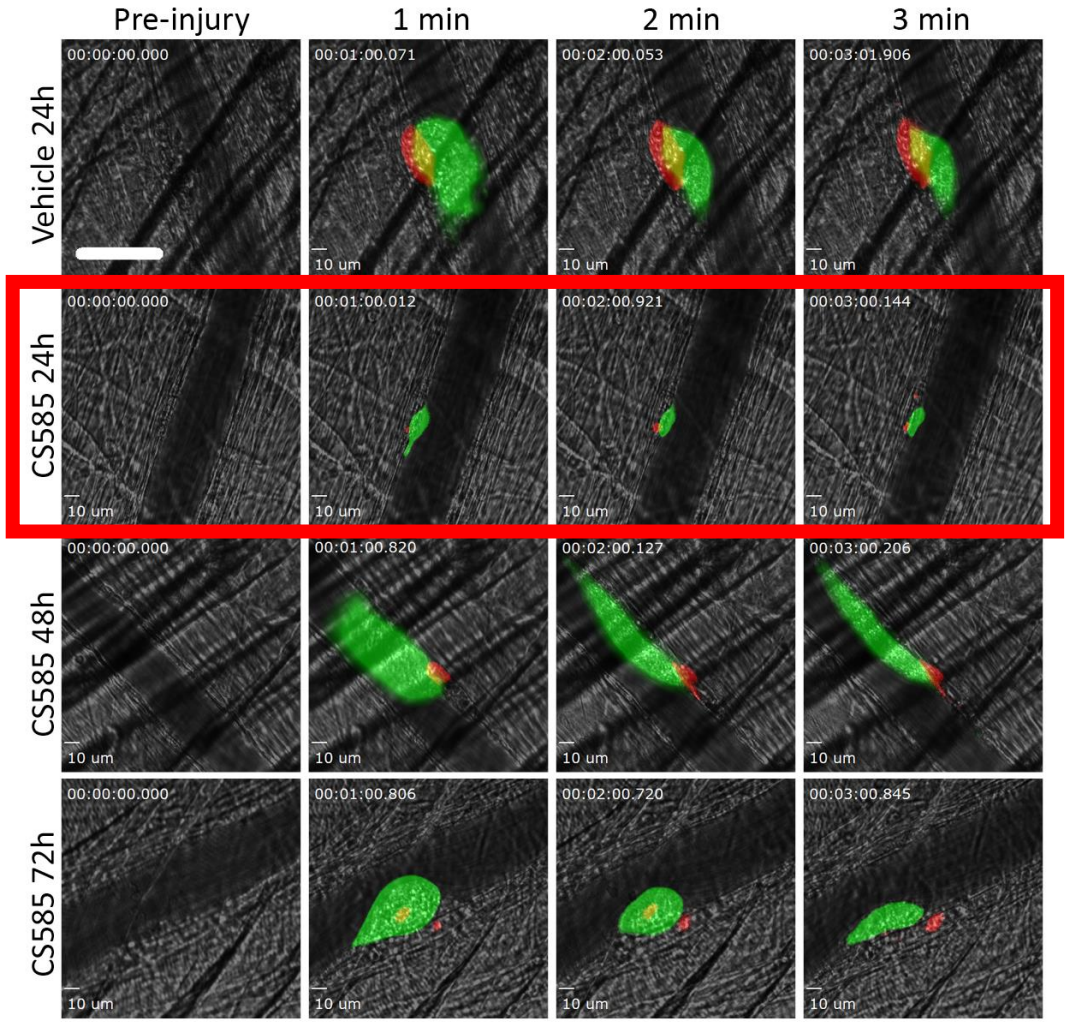


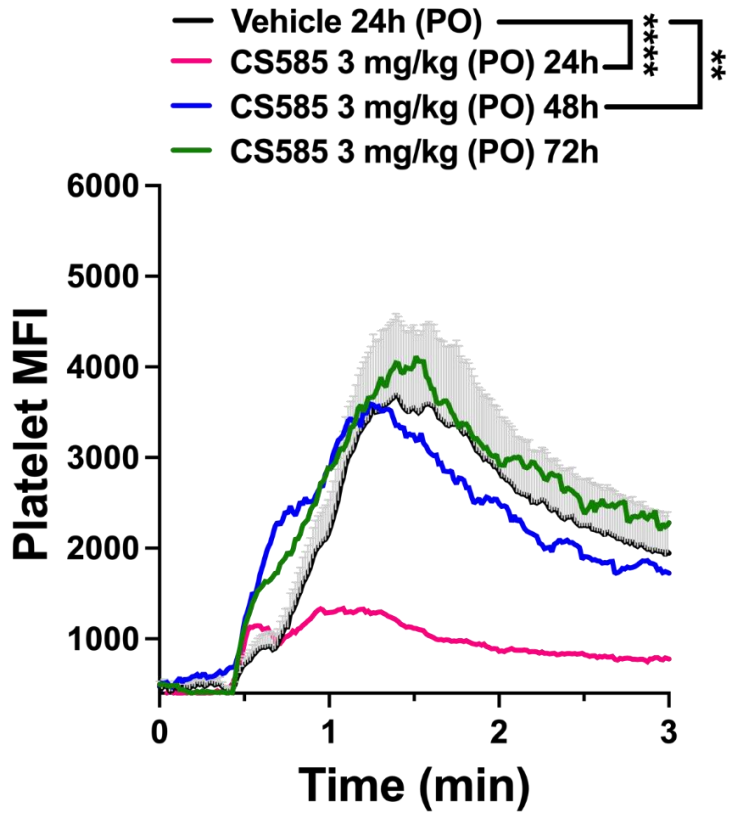


Orally dosed CS585 can inhibit thrombus formation up to 24 hours post-administration

- Single oral administration
- Inhibition with CS585 3 mg/kg:
  - ➢ Platelet activation
  - ➢ Platelet adhesion

❖ Inhibition of thrombosis:
  - ➢ Full inhibition at 24 hours
  - ➢ Full reversal by 48 hours





Stanger et al, Blood. 2023.

Unmet need in rare thrombotic diseases

- Patients suffer from a number of thrombotic diseases and syndromes for which no or limited treatments exist
  - ITP
    - Immune thrombocytopenia or idiopathic thrombocytopenic purpura
    - Rare autoimmune blood disorder that causes low platelet count, bleeding, and thrombosis
    - Immune system mistakenly attacks platelets
  - HITT
    - Heparin-induced thrombocytopenia and thrombosis
    - Rare disease where patients taking heparin produce an antibody that then binds to and activates platelets resulting in bleeding and clotting in the blood
    - 25-30% mortality
  - VITT
    - Vaccine-induced thrombocytopenia and thrombosis
    - Vaccines produce antibodies that activate the platelets and cause clots in the organs
  - APS
  - Antiphospholipid syndrome
  - Antiphospholipid (aPL) antibodies are produced and cause activation of immune system and platelets resulting in NETosis (neutrophil extracellular traps in the blood) and platelet-mediated thrombosis
  - Results in clotting in the microvasculature and multi-organ failure

Stanger et al, Blood. 2023.

Best potential fit for CS585 in preventing thrombosis

- ITP
  - Platelets involved and are a key aspect of the disease
  - Challenges focused on nature of disease, its acute onset and resolution, ambiguous nature of the mechanism of action

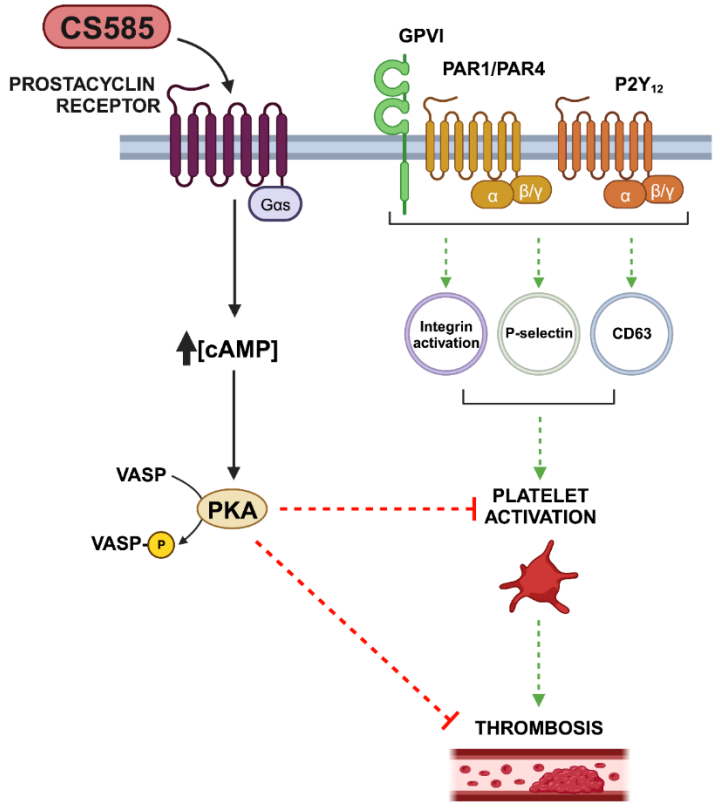
- HITT
  - Platelets are the key to this disease, but also involves immune cells and endothelium
  - With the shift from unfractionated heparin to low molecular weight heparin and FXa inhibitors, the incidence of HITT will continue to decrease

- VITT
  - Recognized for many years, but most prominently observed during the COVID-19 pandemic with non-mRNA derived vaccines such as that produced by Astra Zeneca and Johnson & Johnson
  - With the acceptance of mRNA vaccines on the rise, the incidence of VITT will continue to decrease

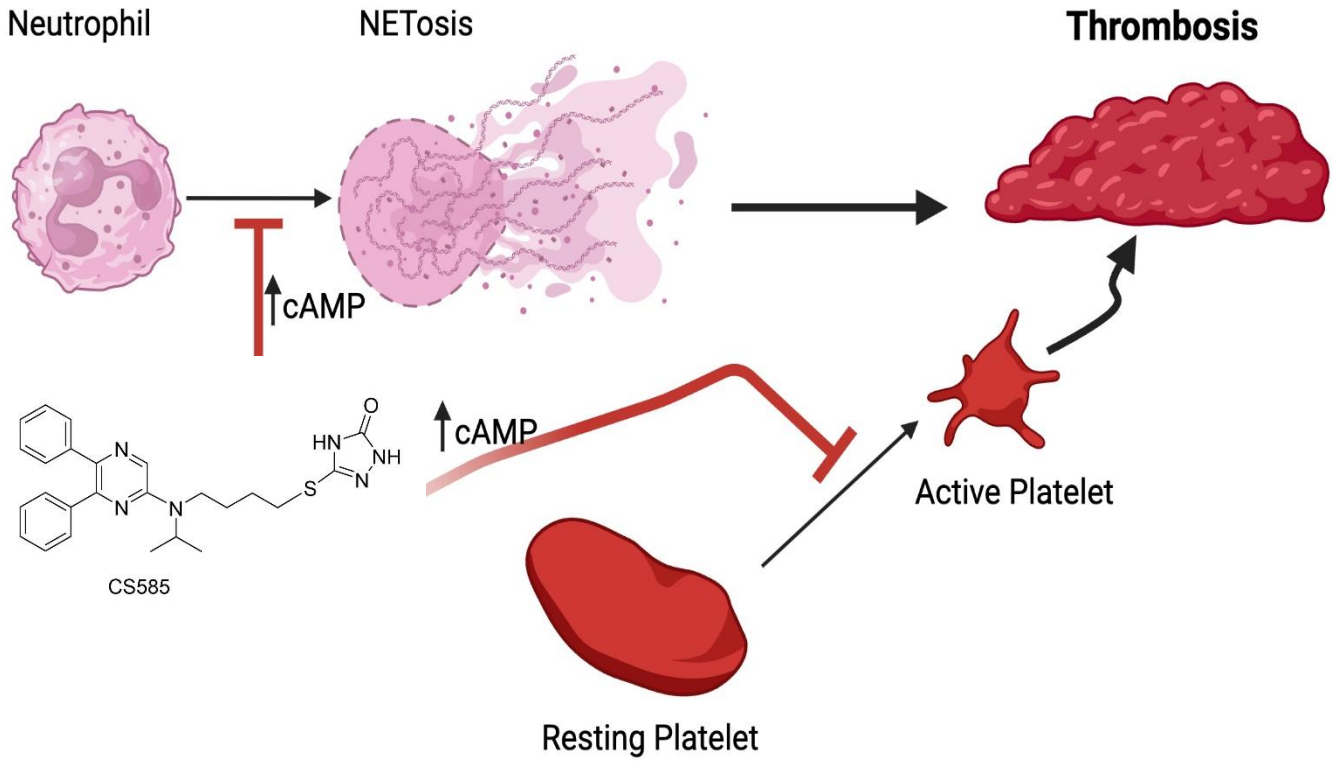
- APS
  - Hallmark of APS is a decreased level of cAMP in the neutrophils resulting in immune cell activation and NETosis
  - There is currently no treatment for APS and the microvasculature of the organs deteriorate over time causing organ failure
  - Pathology of APS is dependent on immune cell and platelet activation
  - Only treatment is anticoagulant with following effectiveness:
    - Only 80% effective for prevention of thrombosis in large vessels
    - NO protection from thrombosis in microvasculature in major organs
    - Syndrome leads to eventual organ dysfunction and failure

Stanger et al, Blood. 2023.

CS585 selectively targets the IP receptor to increase cAMP in the cell



❖ **CS585, by increasing cAMP, prevents neutrophil activation, platelet activation, and progression of APS**



Summary

- Prevalence:
  - 1 in 2,000 people exhibit some form of APS
  - **Responsible for up to 1% of thrombosis globally**
  - 20% of people younger than 50 who have a stroke have APS
  - Reported to be 10 times more frequent in women than men

  Unmet need
  - Only available treatment is vitamin K antagonist
    - Only effective to prevent large vessel thrombosis in 80% of patients
    - *Not effective for prevention of microvascular thrombosis*

  - **Catastrophic APS results in microvascular blood clots leading to organ dysfunction and failure**

❖**CS585 has significant potential as a novel therapeutic for limiting clotting and neutrophil activation in the blood :**

- ***APS is an ideal disease target for CS585***
  - *Alterations in cAMP*
  - *Inhibition of neutrophils and NETosis*
  - *Inhibition of platelet activation and thrombosis*

Agenda

Time	Discussion Item	Speaker
14:45	**Next steps for CS1**	**Dr. Rahul Agrawal** *CMO and Head of R&D, Cereno Scientific*
14:55	**Introduction to Fluidda and the innovative Functional Respiratory Imaging technology**	**Jan De Backer** *CEO Fluidda*
15:05	**Short break**	
15:15	**CS014 targeting unmet needs in rare disease IPF**	**Dr. Björn Dahlöf**, *CSO, Cereno Scientific*
15:35	**CS585 being evaluated rare diseases**	**Dr. Michael Holinstat** *Prof. at University of Michigan Medical School; and Director Translation Research, Cereno Scientific*
15:55	**Cereno Scientific - strategic priorities and future outlook**	**Sten R. Sörensen** *CEO, Cereno Scientific*
16:10	**Questions from Audience on site and online**	Moderated by Dr. Rahul Agrawal, *CMO and Head of R&D, Cereno Scientific*
16:25	**Concluding remarks**	**Sten R. Sörensen** *CEO, Cereno Scientific*

Sten R. Sörensen
Chief Executive Officer

Cereno strategic focus and future outlook

Cereno Scientific

Cereno's portfolio is uniquely positioned to make impact in diseases with high unmet medical needs

Program	Target	Indication	Preclinical	Phase I	Phase II	Phase III	Status
CS1	HDACi with disease-modifying potential	PAH					Phase II top-line results in Q3 2024[1] Expanded Access Program initiated in Q1 2024[1]

Note: Progress bars are only an estimation, not to scale.

Source: 1. Cereno Press Release, 21st Feb 2024; 2. Cereno Press Release, 18th June 2024

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CS014	HDACi with disease-modifying potential	IPF					Phase I initiated in Q2 2024[2]
CS585	PRA oral, selective and potent	CVD					Ongoing preclinical development during 2024/25



Note: Progress bars are only an estimation, not to scale.

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Increased focus on rare diseases

- **Strategic fit with Cereno's vision**
  - Significant unmet medical needs
  - High potential to provide significant value to patients
- **Orphan drug status:**
  - Attractive incentives offered to companies developing orphan drugs
  - Exclusivity US, EU (7, 10 yrs)
- **Attractive business model for biotech companies**
  - Shorter development timelines
  - Less capital intense

Cereno has the potential to deliver high treatment value to patients leveraging our pioneering portfolio and disease-modifying approach to address the root cause of such diseases.

Sten R. Sörensen
Chief Executive Officer

Building attractive pipeline for strategic financial & pharma partners

Cereno's assets/portfolio for:

- Co-development
- Out-licensing
- Asset trade sale
- M&A
- Commercialization

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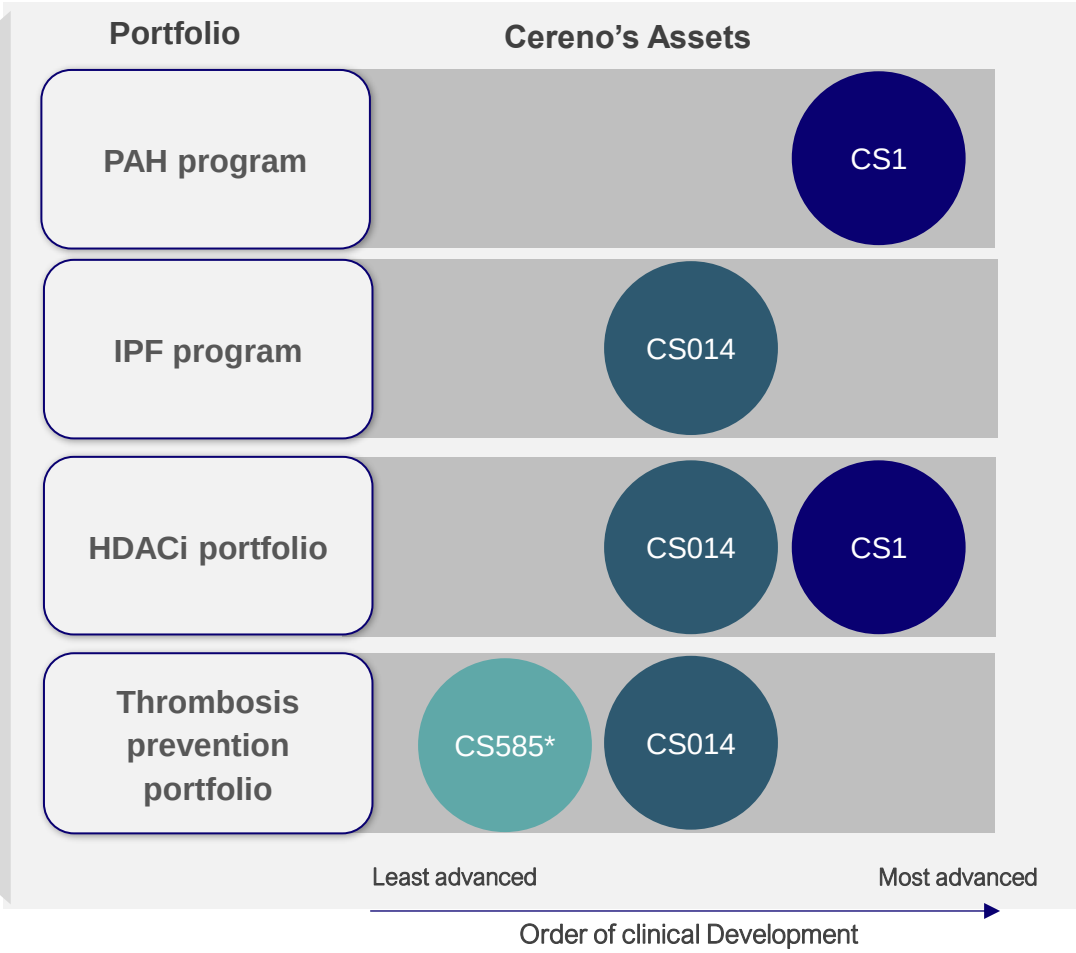


*No Indication has been chosen for CS585. It reflects its potential.

Cereno has pursued several significant strategic shifts starting from a company with a pioneering vision to a clinical stage biotech company

Strategic shifts

- Orphan disease focus
- Broaden the portfolio
- NCE strategy

2019-2023

Strategic shifts

- Multiple clinical assets
- Increased orphan focus
- CS1 phase IIa completion

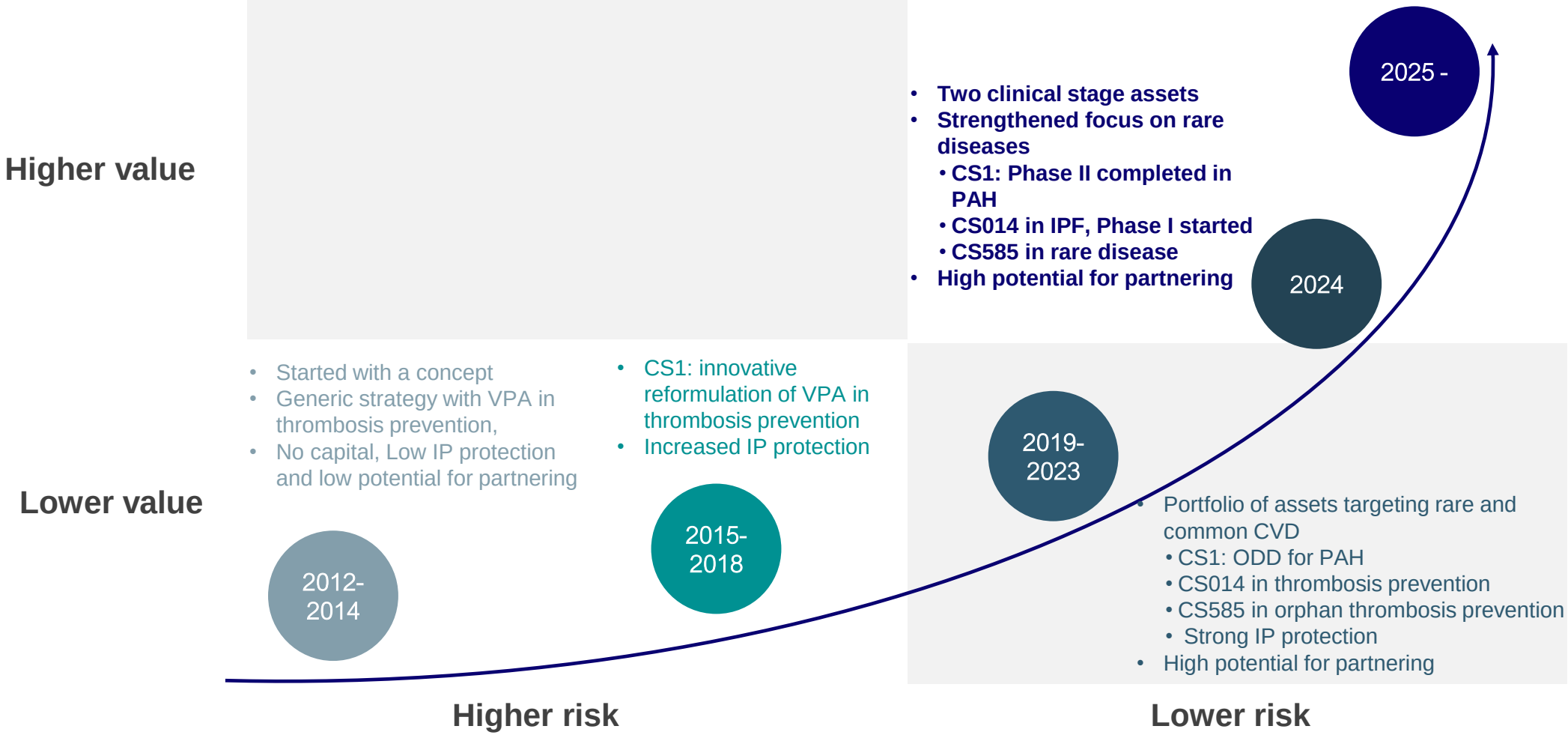
2024

Develop portfolio

Partnering/M&A

Expand shareholder base

Cereno progresses two clinical stage assets and a portfolio targeting diseases with high unmet needs



Cereno has pursued several significant strategic shifts starting from a company with a pioneering vision to a clinical stage biotech company

2019-2023

Strategic shifts

- Orphan disease shift
- Broaden the portfolio
- NCE strategy

2024

Strategic shifts

- Multiple clinical assets
- Increased orphan focus
- CS1 phase IIa completion

2025

Key milestones

- CS1 pivotal FDA approved
- CS014 phase I completion
- EAP long term & Fluidda

2026

Key milestones

- Start of pivotal trial in PAH
- Start of phase II for CS014
- Start of phase I for CS585

Develop portfolio

Partnering/M&A

Expand shareholder base

CS1

Disease-modifying for PAH

CS014

Disease-modifying for IPF

CS585

Thrombosis prevention without increased risk of bleeding

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Q&A

- Please raise your hand if you would like to ask a question
- We will be taking questions from online viewers as well

Cereno Scientific

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Sten R. Sörensen
Chief Executive Officer

Concluding remarks

Cereno Scientific

Enhancing and extending lives of people living with diseases with high unmet medical need

Cereno Scientific

Cereno Scientific

Cereno Scientific develops innovative treatments for rare and common cardiovascular disease. The lead drug candidate, 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. A Phase IIa trial evaluating CS1's safety, tolerability, and exploratory efficacy in patients with the rare disease pulmonary arterial hypertension (PAH) demonstrated that CS1 was safe, well-tolerated and showed a positive impact on exploratory clinical efficacy parameters. CS1 study data, together with preclinical information, is consistent with reversing pathological remodeling. A collaboration agreement with global healthcare company Abbott allowed Cereno to use their cutting-edge technology CardioMEMS HF System in the trial. Since January 2024, we are delighted that the FDA´s Expanded Access Program will enable patients with PAH, a serious life-threatening disease condition, to gain access to CS1 where no comparable alternative therapy options are available. Cereno's pipeline comprises two additional programs in development through research collaborations with the University of Michigan CS014 is a new chemical entity with a multi-fold mechanism of action as an epigenetic modulator – regulating platelet activity, fibrinolysis, and clot stability for the prevention of thrombosis without an increased risk of bleeding as documented in preclinical trials. The drug candidate has also demonstrated a favorable profile in preclinical models of other cardiovascular diseases, such as PAH, with reverse remodeling of pulmonary arterial vessels and effects on vascular fibrosis. On 28th of June, 2024, Cereno initiated a first-in-human Phase I trial of CS014. Preclinical candidate CS585 is an oral, highly potent and selective prostacyclin (IP) receptor agonist that has demonstrated the potential to significantly improve disease mechanisms relevant to cardiovascular disease. While CS585 has not yet been assigned a specific indication for clinical development, preclinical data indicates that it could potentially be used in indications like Pulmonary Hypertension and thrombosis prevention without increased risk of bleeding. CS585 was in-licensed from the University of Michigan in 2023. The Company is headquartered in GoCo Health Innovation City, in Gothenburg, Sweden, and has a US subsidiary; Cereno Scientific Inc. Based in Kendall Square, Boston, Massachusetts, US. Cereno is listed on the Nasdaq First North (CRNO B). The Certified Adviser is Carnegie Investment Bank AB, certifiedadviser@carnegie.se. More information is on www.cerenoscientific.com.

Cereno Scientific

Enhancing and extending lives of people living with diseases with high unmet medical need

Cereno Scientific