SILENCE THERAPEUTICS

Corporate Presentation

November 2024

Forward-Looking Statements

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Silencing diseases through precision engineered medicines created with proprietary siRNA technology

Silence At a Glance

Advancing Clinical Programs

- **Zerlasiran** (Cardiovascular Disease) – phase 2 program targeting elevated Lp(a) - a genetic risk factor for CVD impacting up to 20% of the world's population
- **Divesiran** (Hematological Disorders) – phase 1/2 program in polycythemia vera – a rare blood cancer with significant unmet needs

Proprietary siRNA Technology Platform

- **Broad utility** targeting both rare and common genetic diseases
- **siRNA** technology is **durable** and **reversible**
- Early-stage **liver-focused RNAi programs** have shown **higher likelihood of approval** vs. industry average

Collaborations & Financials

- **Collaborations** further **expand pipeline** and represent **billions** in potential milestones
- **Analyst coverage**: Morgan Stanley, William Blair, BMO Capital Markets, Jefferies, HC Wainwright and Chardan
- **Solid financial position** – projected cash runway into 2026

Lp(a) = Lipoprotein(a) ; CVD = Cardiovascular disease

Evolution of Silence

1998

siRNA work begins in our Berlin research labs

2002

siRNA technology

First core patent application on siRNA technology

2005-2007

SILENCE THERAPEUTICS

AIM listing, company named **Silence Therapeutics plc**

2009-2015

LNP-siRNA expertise

2016-2021

mRNAi GOLD™

- Focus shifted to GalNAc siRNA
- Robust IP protection
- Nasdaq listing

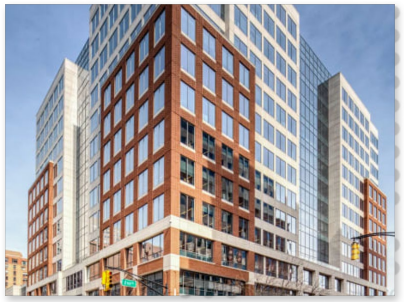
PRESENT

LIVER

Progression of our **pipeline into the clinic** and multiple **big pharma partnerships**

LNP: lipid nanoparticle
siRNA: short interfering RNA

Our Global Footprint



NEW JERSEY
US OFFICE



LONDON
COMPANY HQ



BERLIN
R&D OPERATIONS

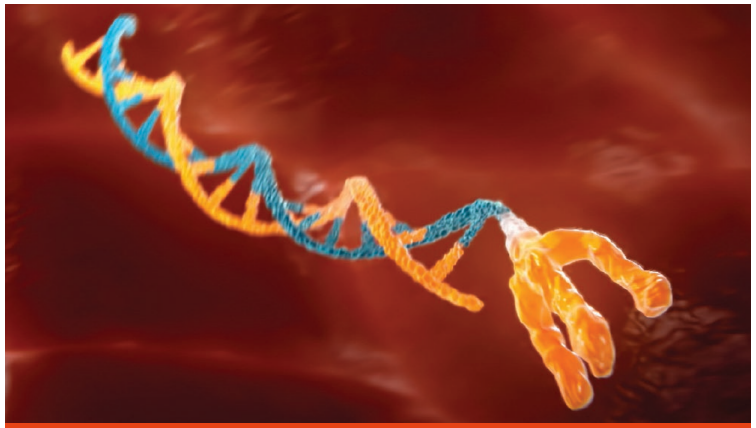
~120 EMPLOYEES WORLDWIDE

Our Toolbox Considers all Elements of siRNA and Ligand Design



siRNA molecule

- siRNA matched to target gene
- Silence has developed chemical modification patterns that enhance stability and improve activity



Linker

- Silence has developed proprietary linkers, enabling the attachment of targeting ligands to the siRNA molecule



GalNAc Ligand (delivery tool)

- GalNAc ligand delivers molecule to specific liver tissues/cells
- Highly targeted to liver

Continuous Fine-Tuning to Further Improve Performance

Our Strategy to Maximize Our mRNAi GOLD™ Platform

PIPELINE

Wholly owned programs that focus and leverage the company's expertise in specific areas with the most opportunity

Partnered programs provide collaboration for a broader reach and potential source for non-dilutive capital

Strategy balances risk and creates more opportunities

mRNAi GOLD™ Proprietary Pipeline

	Indication	Target	Discovery	Preclinical	Phase I	Phase II	Phase III
Zerlasiran (SLN360)	Cardiovascular Disease	LPA					
Divesiran (SLN124)	Polycythemia Vera (PV)	TMPRSS6					
SLN-COMP-1	Complement-mediated Diseases	Undisclosed					
SLN-COMP-2		Undisclosed					
SLN-HAN-1*	Undisclosed						
SLN-HAN-2*	Undisclosed						
Multiple Programs	Undisclosed						

*Silence retains exclusive rights to this program outside of the China region, including Hong Kong, Macau and Taiwan.

Collaborations Further Expand Pipeline and Represent Billions in Potential Milestones

AstraZeneca

Collaboration to discover, develop and commercialize siRNA therapeutics for cardiovascular, renal, metabolic and respiratory diseases

- Upfront cash payment of $60 million and an equity investment of $20 million
- Up to $4 billion in potential milestones plus tiered royalties for a total of 10 targets
- First undisclosed target entered the clinic in February 2024

翰森制药
HANSOH PHARMA

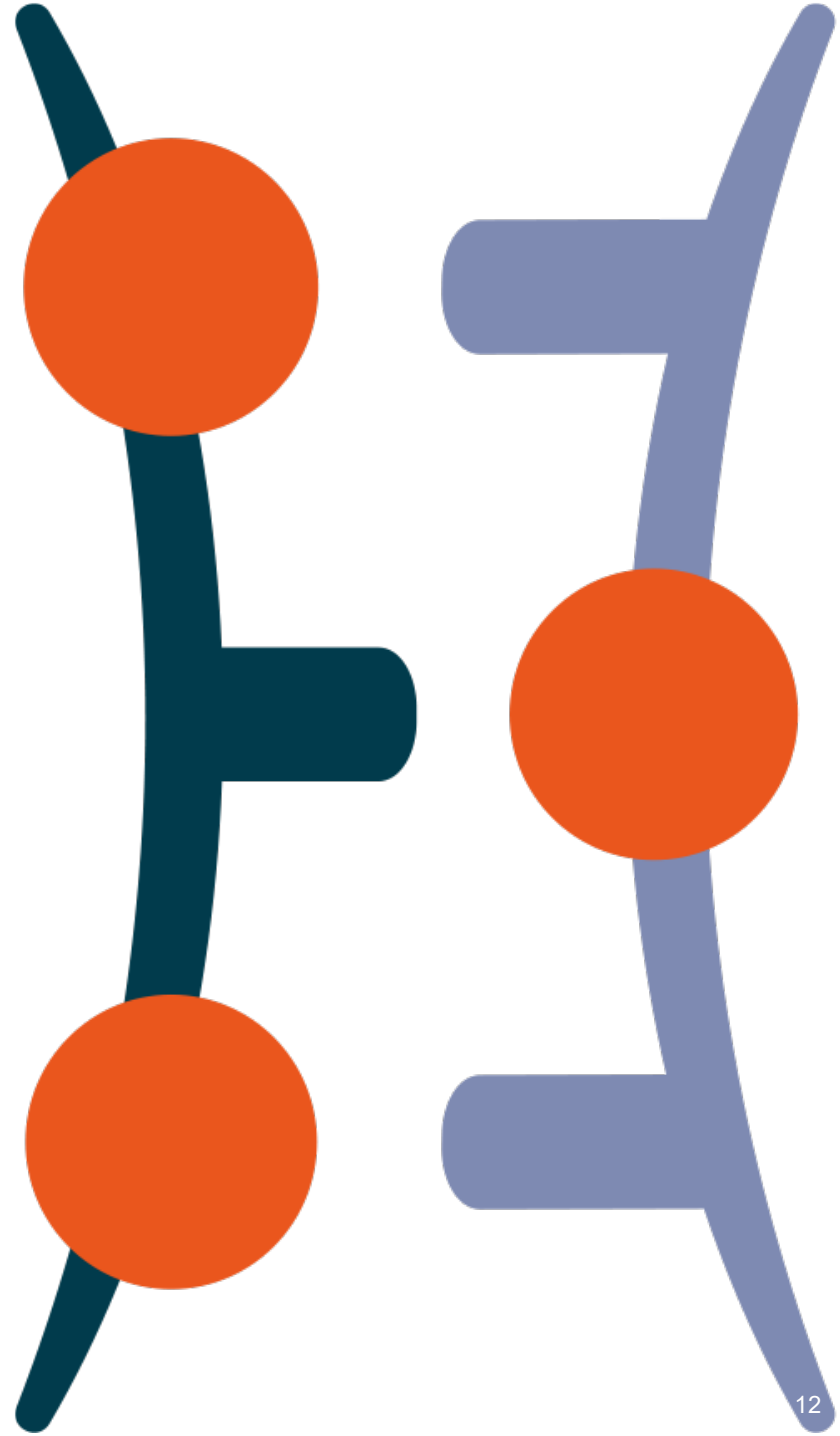
Collaboration to develop siRNA therapeutics for undisclosed targets

- Upfront cash payment of $16 million and up to $1.3 billion in potential milestones plus royalties
- Silence has exclusive rights to 2 targets in all territories except China region; Hansoh has global rights to a third target

2024 Key Strategic Priorities

1. Accelerate Lead Proprietary Clinical Programs
2. Advance Partnered Programs
3. Advance and Expand Proprietary Pipeline

Clinical Programs





Zerlasiran

Cardiovascular Disease

Zerlasiran Targets Lp(a): an Independent Risk Factor for Cardiovascular Disease

- At least 20% of the global population has high Lp(a) defined as ≥125 nmol/L (~50 mg/dL)[1]
- Lp(a) levels are genetically determined
- Recognized as a major untreated risk factor in cardiovascular disease
- Lp(a) levels are not significantly modifiable by approved medicines or lifestyle changes

Zerlasiran Has the Potential to Address Major Unmet Needs in Cardiovascular Disease

mg/dL: milligrams per deciliter, nmol/L: nanomoles per liter (approximate conversion factor of 2.5)

1. Lau, F. D., & Giugliano, R. P. (2022). Lipoprotein (a) and its significance in cardiovascular disease: a review. Jama Cardiology, 7(7), 760-769.

Lp(a) is an Inherited Cause of Early Cardiovascular Disease

Patient Testimonials

"I'd been on statins from when I was 20, I had a reasonably healthy lifestyle, I shouldn't be having three stents and a heart bypass before I'm 50"

– John-Paul



"I got tested and my number [Lp(a)] came back as 921. Now, 75 is considered bad. I have a sister, Joan, who I lost at the age of 44 to a heart attack… She was being treated for back pain but wound up passing away at 44 from a heart attack. I just lost in May my younger sister, Barbara, at the age of 55...**"**

- Steve



Zerlasiran Has Substantial Market Potential

High Cholesterol vs High Lp(a) in Cardiovascular Disease

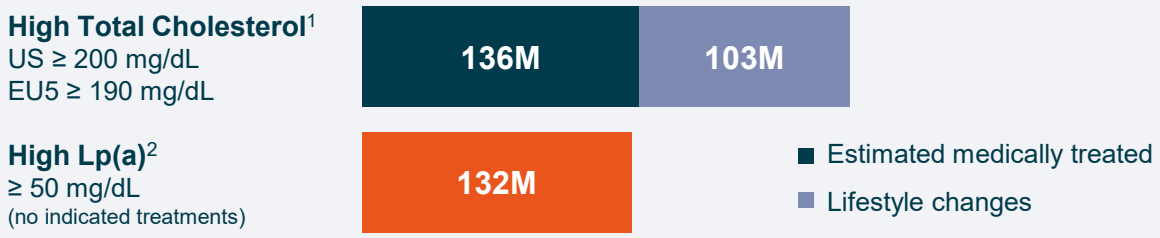
High Cholesterol is a **Modifiable Risk Factor** → Lifestyle changes **can** have a positive impact

High Lp(a) is a **Genetic Risk Factor** → Lifestyle changes **have no effect** on Lp(a) levels

Similar Medically Treated Population

Patients with High Total Cholesterol vs. High Lp(a)

US + EU5 Markets



Blockbuster Potential

Sales of Cholesterol-Lowering Drugs Peaked at >$30B[3,4]

Lipitor® (atorvastatin)	**Crestor®** (rosuvastatin)	**Zocor®** (simvastatin)
$12.9B peak sales	**$7.0B** peak sales	**$5.2B** peak sales

[1] Datamonitor Healthcare | Informa 2018, [2] Varvel et al Arterioscler Thromb Vasc Biol. 2016;36:2239, Tsimikas et al. Atherosclerosis 2020;300:1, Nordestgaard et al. Eur Heart J. 2010;31:2844,
[3] Biomedtracker, Internal Analysis; [4] Kidd, J., Nat Rev Drug Discov. 2006;5(10):813

CV Event Risk Significantly Increases with High Lp(a) Levels

Substantial Risk of CV Event at Lp(a) ~90 mg/dL

Event	Increased Risk
Heart Attack[1]	2 - 3x
Aortic Stenosis[2]	2 - 3x
Heart Failure[3]	1.6 - 1.8x
Ischemic Stroke[4]	1.2 - 1.6x
Mortality[5] (all cause/CV)	1.2 - 1.7x

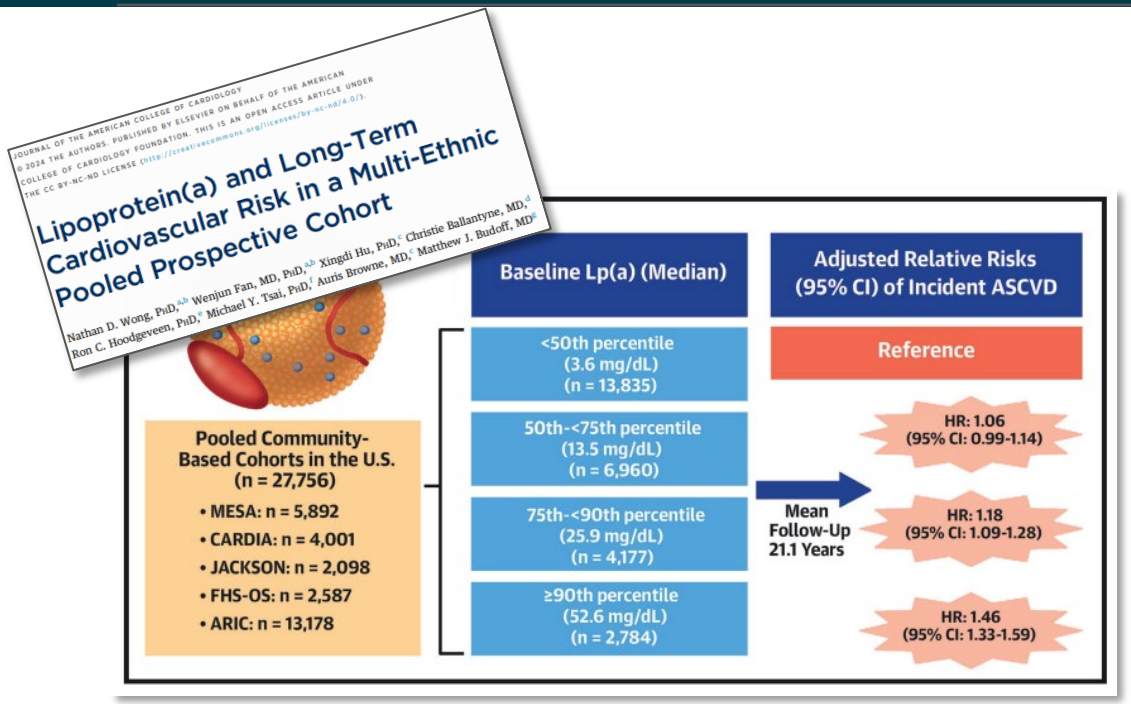
780 Million Worldwide with >90 mg/dL Lp(a)

Lp(a) level:	>50 mg/dL	>90 mg/dL
Prevalence[6]	~20%	~10%
USA	66m	33m
EU	103m	51m
Globally	1,560m	780m

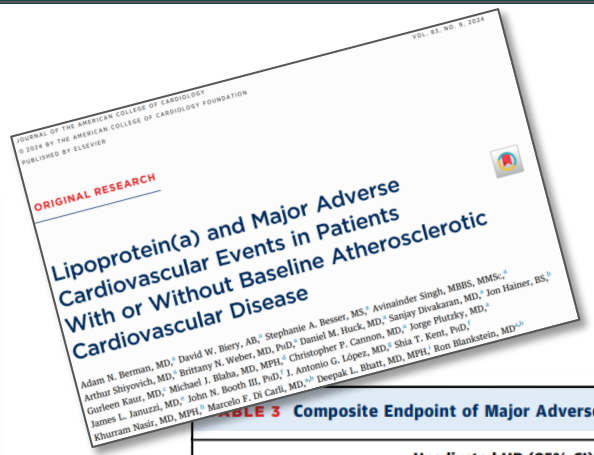
Populations: USA 328.2 million, EU 513.5 million (incl. UK), Global 7,800 million

[1] Kamstrup et al. Circulation. 2008;117:176, Kamstrup et al. JAMA. 2009;301(22):2331, [2] Kamstrup et al. J Am Coll Cardiol. 2014;63(5):470, [3] Kamstrup et al. JACC Heart Fail. 2016;4(1):78, [4] Langsted et al. J Am Coll Cardiol. 2019;74(1):54,
[5] Langsted et al. Eur Heart J. 2019;40(33):2760, Arsenault et al. JAMA Netw Open. 2020;3(2):e200129, [6] Varvel et al Arterioscler Thromb Vasc Biol. 2016;36:2239, Tsimikas et al. Atherosclerosis. 2020;300:1, Nordestgaard et al. Eur Heart J. 2010;31:2844

Several 2024 Analyses Show an Inflection in CV Risk Beginning at Lp(a) Levels as Low as 75nmol/L (30 mg/dL)



Wong et al 2024



Lp(a) percentile groups	Lp(a) levels
1st-50th	0-41 nmol/L
51st-70th	42-111 nmol/L
71st-90th	112-215 nmol/L
91st-100th	≥216 nmol/L

TABLE 3 Composite Endpoint of Major Adverse Cardiovascular Event for Individuals With and Without Baseline ASCVD

	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
1st-50th percentile	Reference	—	Reference	—
51st-70th percentile	1.18 (1.09-1.28); $P < 0.001$	1.14 (1.05-1.24); $P = 0.002$	1.11 (0.92-1.35); $P = 0.265$	1.09 (0.90-1.32); $P = 0.354$
71st-90th percentile	1.26 (1.15-1.37); $P < 0.001$	1.21 (1.11-1.32); $P < 0.001$	1.24 (1.03-1.49); $P = 0.024$	1.17 (0.97-1.41); $P = 0.096$
91st-100th percentile	1.27 (1.14-1.43); $P < 0.001$	1.26 (1.12-1.41); $P < 0.001$	2.04 (1.63-2.55); $P < 0.001$	1.93 (1.54-2.42); $P < 0.001$

Values are n/N (%) unless otherwise indicated. [a]Adjusted for age, sex, self-reported race/ethnicity, hypertension, chronic kidney disease status, non-Lp(a) hyperlipidemia, diabetes, insulin use (in diabetic individuals), and smoking status.
MACE = major adverse cardiovascular events; other abbreviations as in Table 2.

Beman et al 2024

- ✓ Lp(a) at levels well below currently accepted risk thresholds correlate with increased CV risk
- ✓ Suggests a wider patient pool could benefit from future preventive therapies

Major CV Societies Recommending Lp(a) Testing

2022 European Atherosclerosis Society Consensus Statement

Lp(a) should be measured at least once in adults

2021 Canadian Cardiovascular Society (CCS)

Lp(a) measurement for everyone once in a lifetime

2018 AHA/ACC

Relative indications for its measurement are a family history of premature ASCVD or personal history of ASCVD

2022 ESC/EAS. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement
2018 AHA/ACC: The 2018 American Heart Association/American College of Cardiology (AHA/ACC) Guideline on the Management of Blood Cholesterol,
2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults

Zerlasiran Phase 1 Program Overview

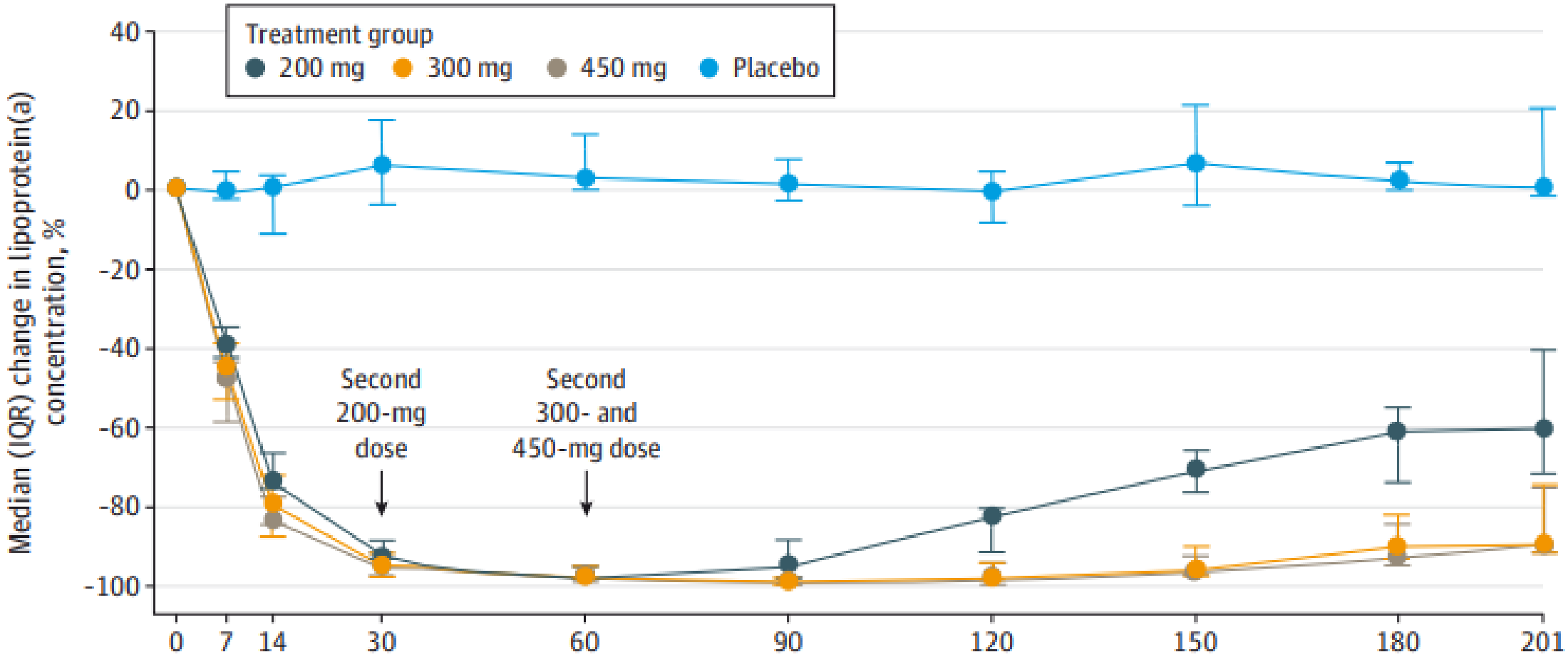
- Evaluated participants with high Lp(a) ≥150 nmol/L
- Healthy volunteers showed Lp(a) reductions up to 98% following a single dose with effects persisting over a five-month period
- ASCVD patients showed Lp(a) reductions up to 99% following repeated doses with effects persisting at 201 days
- Zerlasiran was well tolerated with no serious safety issues



nmol/L= nanomoles per liter; ASCVD = atherosclerotic cardiovascular disease

1. Journal of the American Medical Association (JAMA). April 8, 2024. Single Ascending and Multiple-Dose Trial of Zerlasiran, a Short Interfering RNA Targeting Lipoprotein(a): A Randomized Clinical Trial | Clinical Pharmacy and Pharmacology | JAMA | JAMA Network.

Zerlasiran Produced Significant and Sustained Lp(a) Reductions in Phase 1 Multiple Dose Study



1. Journal of the American Medical Association (JAMA). April 8, 2024. Single Ascending and Multiple-Dose Trial of Zerlasiran, a Short Interfering RNA Targeting Lipoprotein(a): A Randomized Clinical Trial | Clinical Pharmacy and Pharmacology | JAMA | JAMA Network.

Zerlasiran Phase 2 Study Overview

- Evaluated ASCVD patients with high Lp(a) ≥125 nmol/L over 60 weeks
- Study met primary endpoint and demonstrated a highly significant reduction from baseline in Lp(a) compared to placebo to week 36
- Median maximum Lp(a) reduction of approximately 90% or greater was observed during the treatment period
- Well tolerated with no serious safety issues

alpacard 360

Data Support Advancing Zerlasiran into Phase 3 with 300 mg Dose

nmol/L= nanomoles per liter; ASCVD = atherosclerotic cardiovascular disease

1. Silence Therapeutics. June 20, 2024. Silence Therapeutics Announces Positive Topline 48-Week Data from Phase 2 Study of Zerlasiran in Patients with Elevated Lipoprotein(a).



Divesiran

Hematological Disorders

Polycythemia Vera (PV): A Rare Blood Cancer We Are Targeting

- **Myeloproliferative neoplasm characterized by the excessive production of red blood cells (RBCs)**
  - Elevated hematocrit (HCT) is a hallmark of the disease, indicating overproduction of RBCs
- **Serious, chronic disease associated with increased thrombotic and cardiovascular risks[1-3]**
- **Rare disease with ~150,000 in the US and ~3.5m worldwide[4]**
  - Diagnosed commonly in individuals 50-70 years of age
  - Median survival ~20 years

Treatment goal is to control HCT <45% to reduce CV and major thrombotic events

1. NORD Rare Disease Database, Polycythemia Vera. https://rarediseases.org/rare-diseases/polycythemia-vera/ 2. Spivak JL. Ann Hematol 2018; 19(2):1-14. 3. Marchioli R, et al. N Engl J Med 2013; 368:22-33 4.Using 44/100,000 global population: 7,800m, Kattamis, A. et al. Eur J Haematol (2020);

People Living with PV Experience Significant Unmet Needs

Inconsistent HCT Control

- Patients with HCT between 45-50% are ~4x more likely to die from CV causes or major thrombotic events than those <45%[1]
- 78% of patients have uncontrolled HCT with tests ≥45%[2]

Iron Deficiency

- Most patients with PV are iron deficient due to depleted bone marrow iron levels[3]
- Some treatments exacerbate disease-related symptoms by inducing iron deficiency[3,4]

Disease Burden

- Patients with elevated HCT often require frequent phlebotomies to manage condition
- 30-40% of PV patients who receive cytoreductive therapy have a suboptimal response and toxicity issues[5]
- Patients have burdensome symptoms, including fatigue and concentration problems[5]

1. Marchioli et al. 2013 NEJM paper; 2. Verstovsek S, et al. Ann Hematol. 2023 Mar;102(3):571-581; 3. Verstovsek S, et al. Leuk Res. 2017;56:52-59. doi:10.1016/j.leukres.2017.01.032.;4. McMullin MF, et. al. Br J Haematol. 2019 Jan; 184(2): 176-191.; 5. Mesa, R. Clin Adv Hematol Oncol (2017)

Divesiran Has the Potential to Be First siRNA for PV

Divesiran targets *TMPRSS6* and modulates hepcidin – the body's master iron regulator

Proof of mechanism demonstrated in healthy volunteer study

Positive interim results from SANRECO Phase 1 study in PV patients

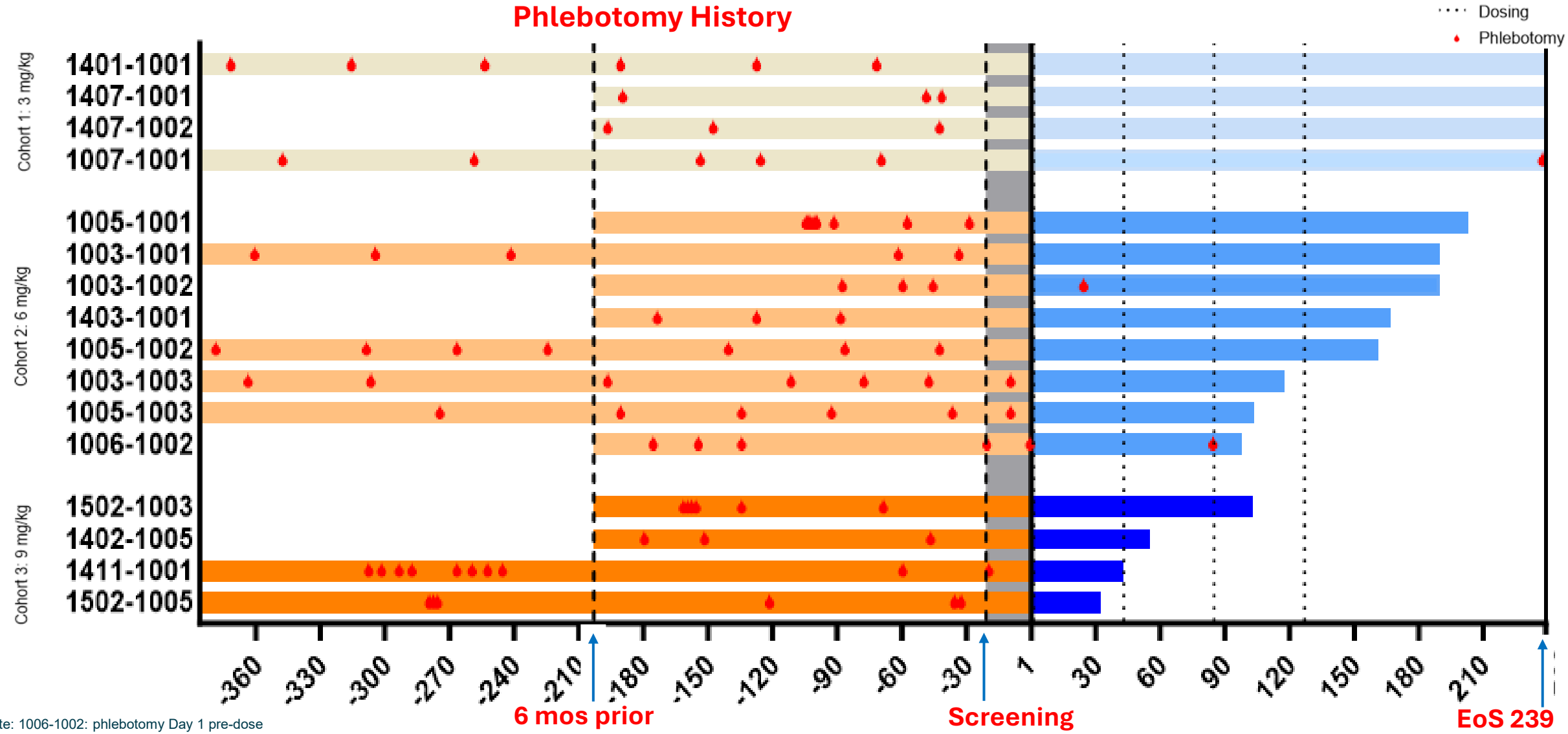
Divesiran has FDA Fast Track and Orphan Drug Designation for PV

SANRECO Phase 1 Study of Divesiran in PV Patients

Design	Open-label, dose-finding study
Key Inclusion Criteria	• PV diagnosis • At least 3 phlebotomies in the last 6 months or 5 in the last year prior to screening • Stable dose of cytoreductive agents allowed • No hematocrit threshold
Dosing & Follow-up	• Evaluating divesiran 3 mg/kg, 6 mg/kg and 9 mg/kg • Administered subcutaneously every 6 weeks for four doses • 16-week follow-up period following the date of the last administered dose • Total duration of study 34 weeks
Enrollment	• 21 patients enrolled • 6 patients at 3 mg/kg, 8 patients at 6 mg/kg and 7 patients at 9 mg/kg



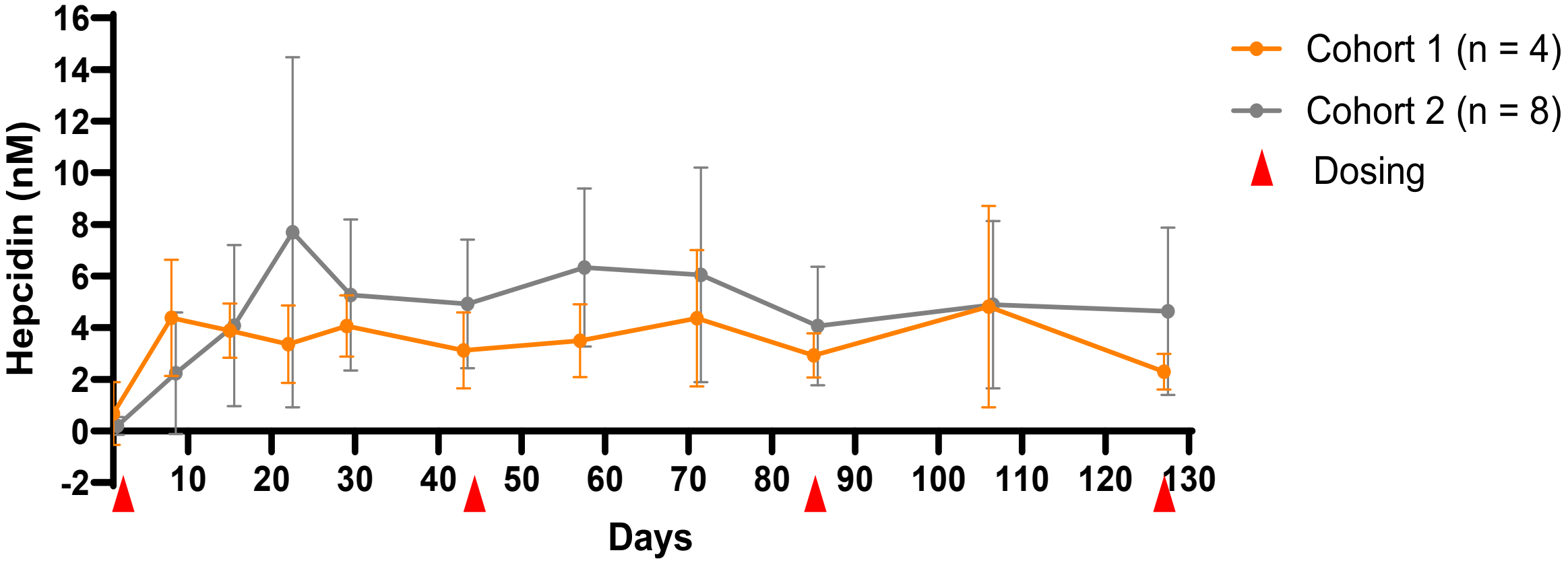
SANRECO Interim Results Showed Divesiran Substantially Reduced Phlebotomy Requirements in PV Patients



Note: 1006-1002: phlebotomy Day 1 pre-dose

1. Silence Therapeutics. June 27, 2024. Silence Therapeutics Announces Positive Results from Ongoing SANRECO Phase 1 Study of Divesiran in Polycythemia Vera Patients; 2. Data based on a cutoff date of March 29, 2024 (16 patients)

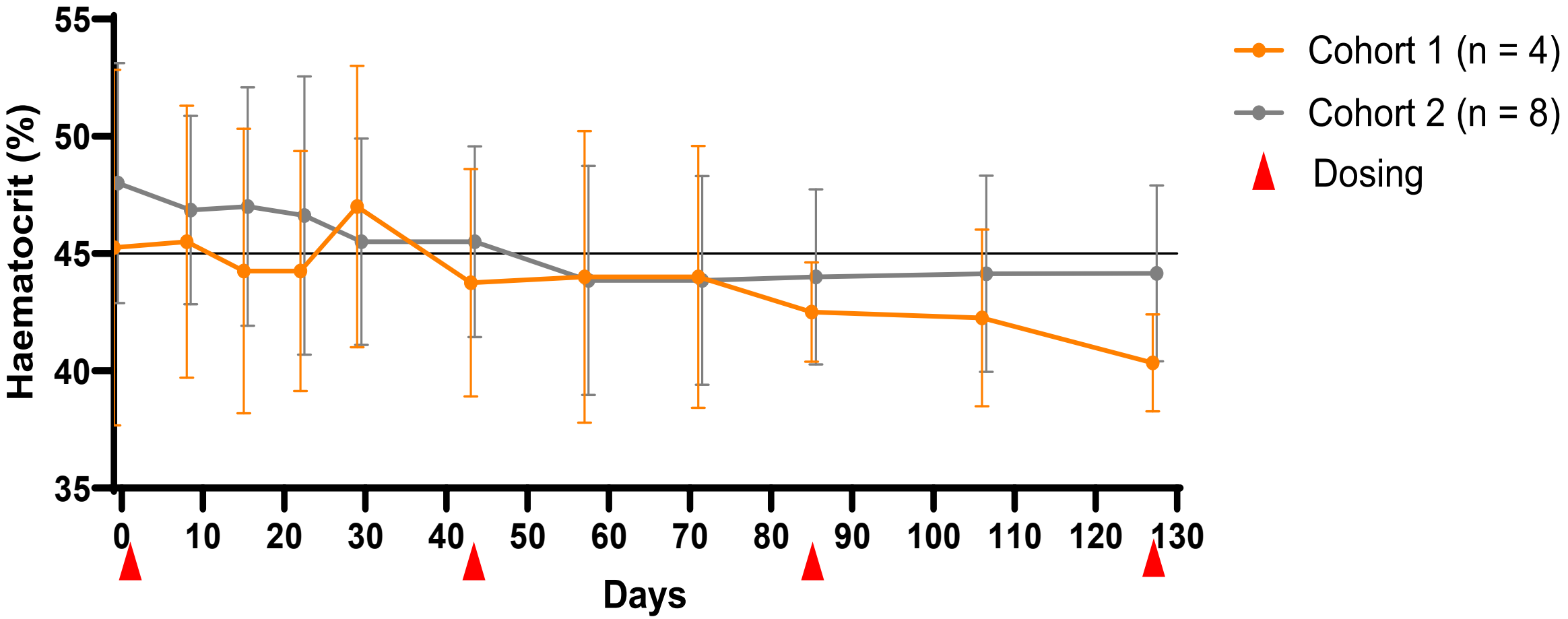
Divesiran Elevated Hepcidin in PV Patients, Demonstrating Robust Target Engagement



Note: Error bars represent +/- 1 SD

1. Silence Therapeutics. June 27, 2024. Silence Therapeutics Announces Positive Results from Ongoing SANRECO Phase 1 Study of Divesiran in Polycythemia Vera Patients; 2. Data based on a cutoff date of March 29, 2024 (16 patients)

Divesiran Treated PV Patients Achieved Target HCT Levels of 45% or Below



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1. Silence Therapeutics. June 27, 2024. Silence Therapeutics Announces Positive Results from Ongoing SANRECO Phase 1 Study of Divesiran in Polycythemia Vera Patients; 2. Data based on a cutoff date of March 29, 2024 (16 patients)

Divesiran Has Been Well Tolerated To-Date

- No drug related SAEs
- No withdrawals due to divesiran related AEs
- Mild injection site reactions (ISRs) have been reported, all grade one and fully resolved

Positive Phase 1 Interim Results Support Advancing to Phase 2 By Year-End

1. Silence Therapeutics. June 27, 2024. Silence Therapeutics Announces Positive Results from Ongoing SANRECO Phase 1 Study of Divesiran in Polycythemia Vera Patient**s; 2.** Data based on a cutoff date of March 29, 2024 (16 patients)

Key Investment Highlights

Advancing multiple wholly owned clinical programs

- Zerlasiran targeting large CV market with multi billion-dollar potential
- Divesiran poised to be the first siRNA for PV

Progressing existing partnerships and new opportunities

- AstraZeneca collaboration now in the clinic with first undisclosed target
- Advancing targets under Hansoh collaboration
- Growing partnering interest around our GOLD platform

Proprietary siRNA technology platform with substantial untapped opportunity

- Advancing multiple early-stage programs with promising pre-clinical data in areas of high unmet need



Silencing diseases through precision engineered medicines created with proprietary siRNA technology

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