SILENCE THERAPEUTICS

Corporate Presentation

November 2025

Forward-Looking Statements

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Silencing diseases through precision engineered medicines created with proprietary siRNA technology

Key Milestones Achieved This Year

- ✓ Presented updated SANRECO Phase 1 data at EHA 2025 further supporting potential for divesiran as first-in-class siRNA in PV
- ✓ Achieved rapid enrollment in SANRECO Phase 2 PV study - topline results expected in 3Q 2026
- ✓ Completed core Phase 3 readiness activities for zerlasiran in high Lp(a)
- ✓ Advanced extra-hepatic cell targeting of siRNA with promising initial data

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

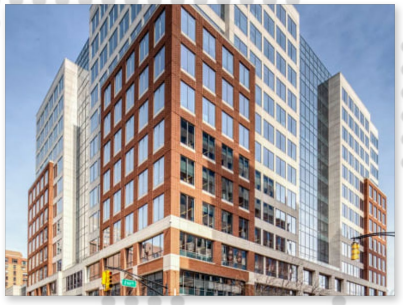
PRESENT

LIVER

Progression of our **pipeline into the clinic** and multi-target **collaboration with AstraZeneca**

LNP: lipid nanoparticle
siRNA: short interfering RNA

Our Global Footprint



NEW JERSEY
US OFFICE

LONDON
COMPANY HQ

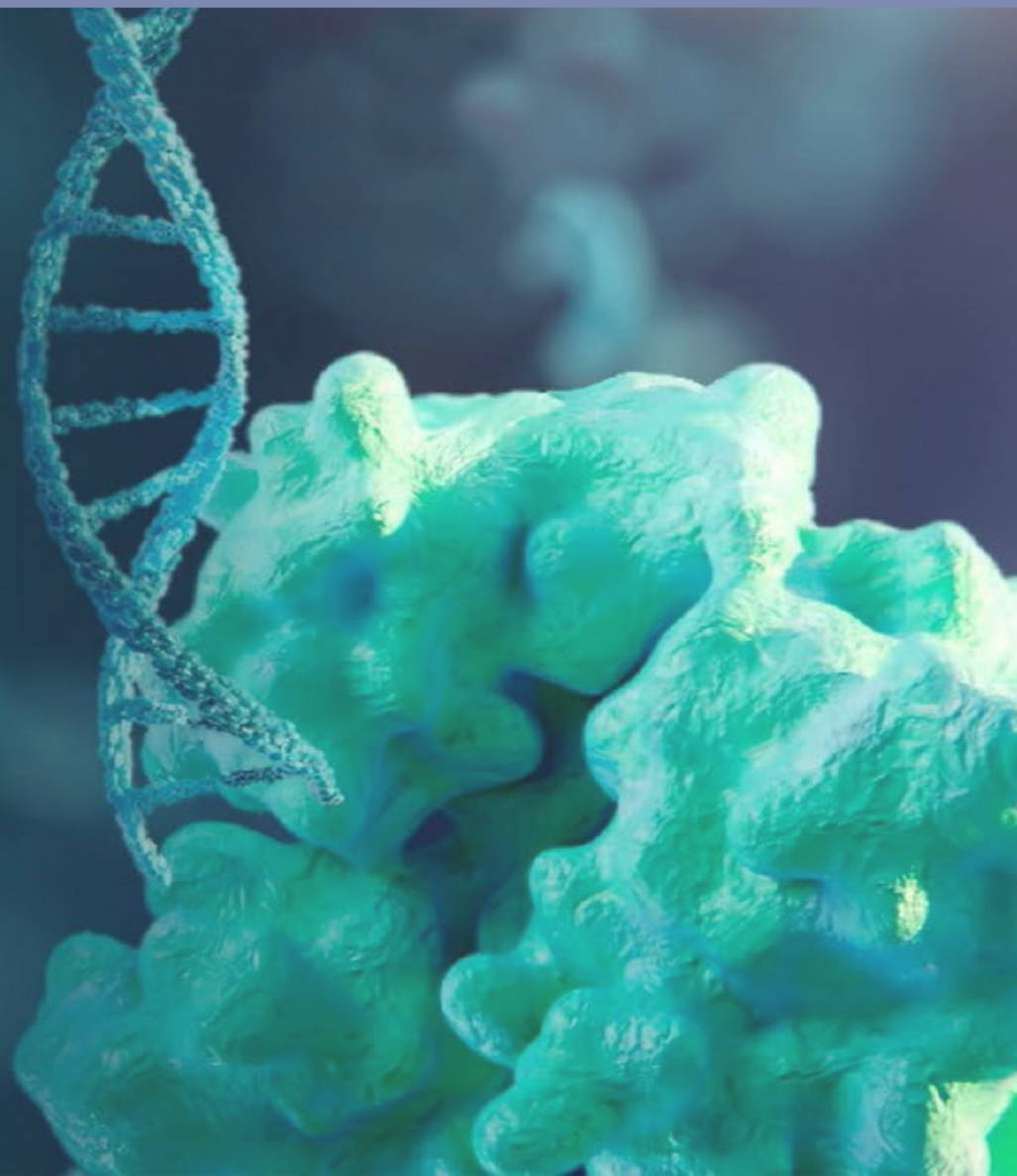
BERLIN
R&D OPERATIONS

siRNA expertise spanning drug discovery, design and clinical development

Precision Engineered Medicines to Silence Disease

The Silence siRNA Platform

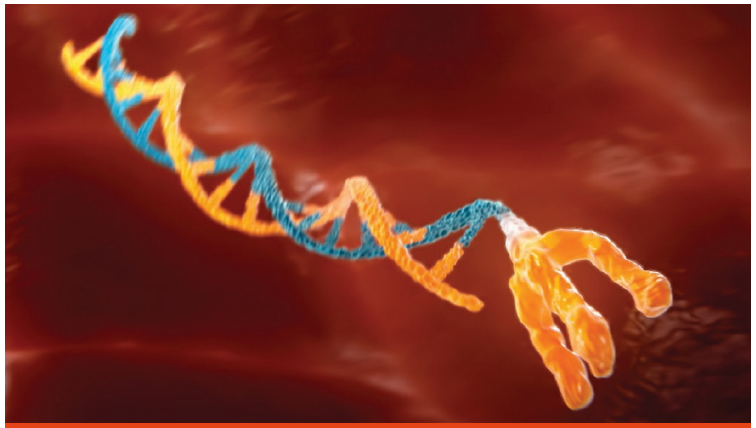
- **Precise:** each siRNA is uniquely designed to only bind to the target mRNA, which can reduce potential for side effects
- **Broad Utility:** targeting both rare and common diseases
- **Durable, yet Reversible:** siRNA therapies can achieve long lasting effects without permanently altering the gene
- **Clinical Results:** demonstrated in multiple areas of high unmet need



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

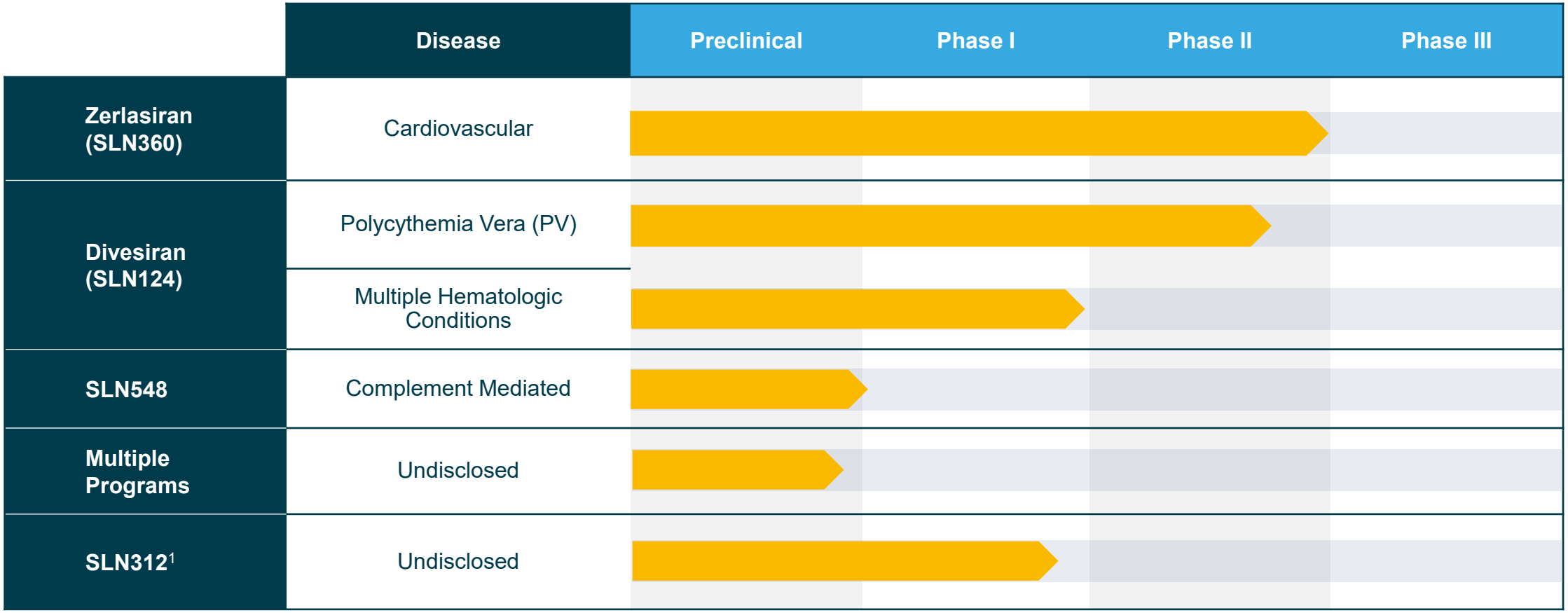
- Silence has developed proprietary linkers, enabling the attachment of targeting ligands to the siRNA molecule

GalNAc Ligand (delivery tool)

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

Continuous Fine-Tuning to Further Improve Performance

mRNAi GOLD™ Development Pipeline



[1] Licensed to AstraZeneca with milestones and royalties as part of ongoing collaboration to discover, develop and commercialize siRNA therapeutics for cardiovascular, renal, metabolic and respiratory diseases using Silence's mRNAi GOLD™ platform

Divesiran

Polycythemia Vera

Polycythemia Vera (PV) is a Rare Blood Cancer with Significant Unmet Needs

- **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 Have 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]
- Most 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]

"The PV aspect means that you have to have phlebotomies regularly and I think the most crippling thing about that is the fatigue."
– Nona Baker

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 is a First-in-Class siRNA for PV with Unique MOA

Compelling Ph1 efficacy & safety

Infrequent Dosing Profile

Opportunities for Improved Quality of Life

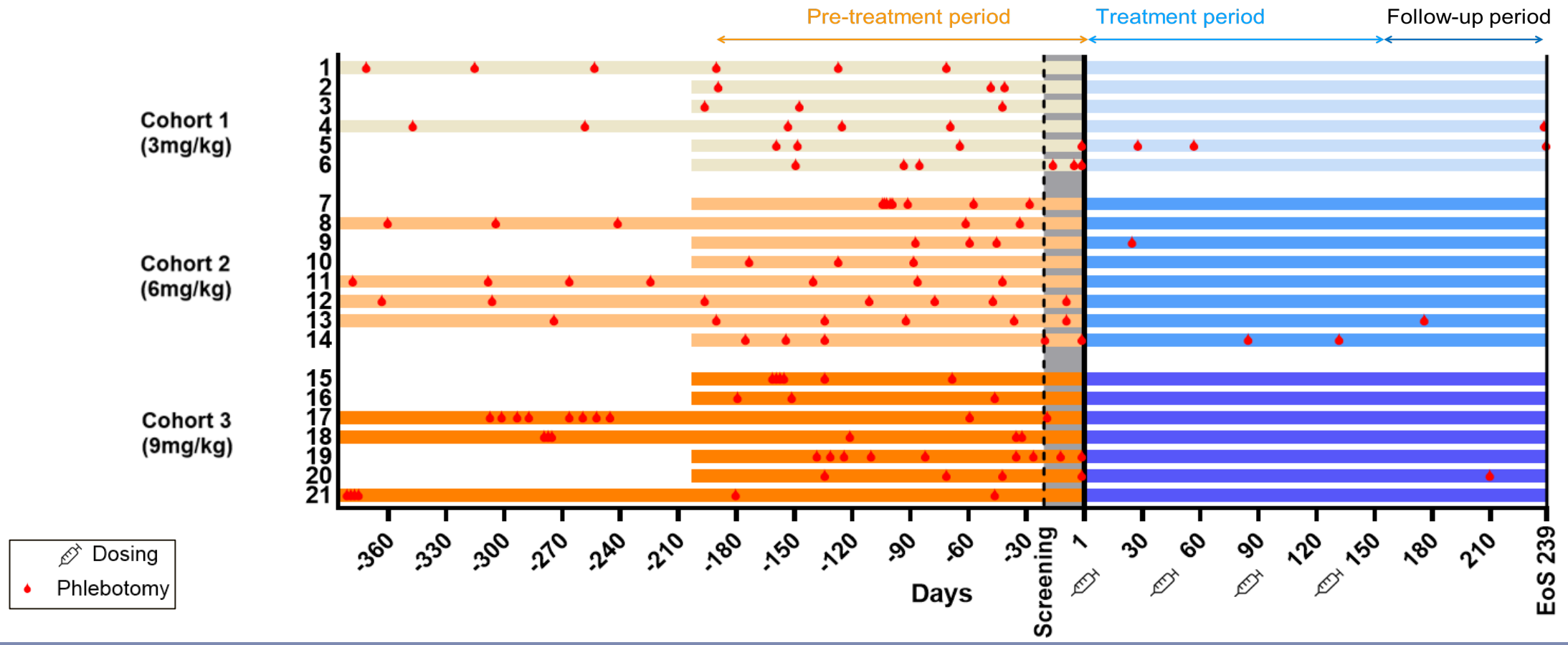
Opportunities for Differentiation

SANRECO Phase 1 Study Overview

Study Completed in February 2025

Design	• Open-label, dose-finding study of divesiran in 21 PV patients • 6 patients at 3 mg/kg, 8 patients at 6 mg/kg and 7 patients at 9 mg/kg
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 HCT threshold
Dosing & Follow-up	• Administered subcutaneously Q6W for four doses • 16-week follow-up period following the date of the last administered dose • Total duration of study 34 weeks
Key Objectives	• Safety and tolerability • Assessment of the number of phlebotomies at 3 intervals (pre-treatment, treatment and follow-up)

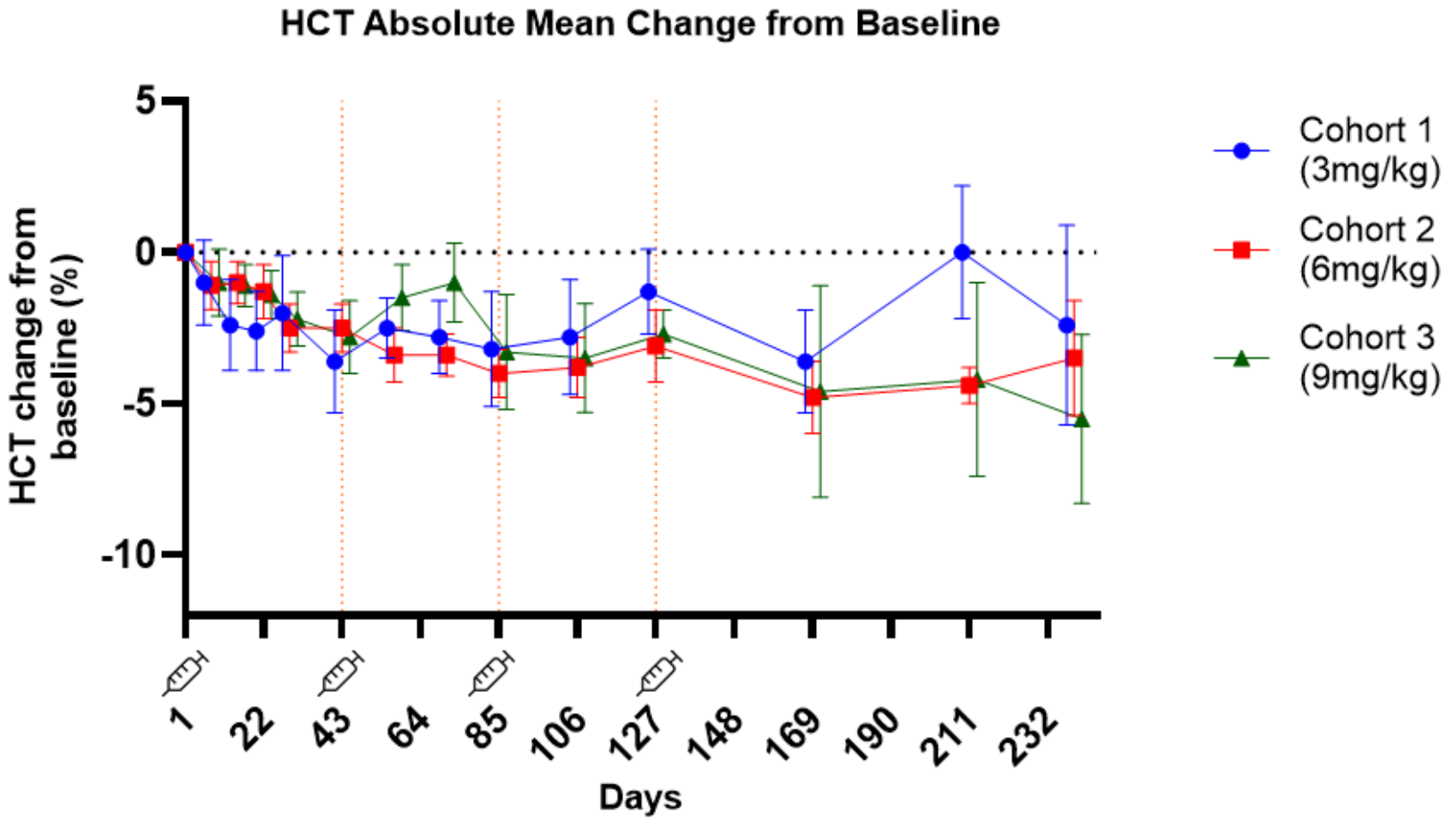
Divesiran Reduced Phlebotomy Frequency in All PV Patients



79 Phlebotomies Prior to Dosing, 5 in Treatment Period and 4 in Follow-up; No Well-Controlled Patients (HCT<45% at Baseline) Required a Phlebotomy

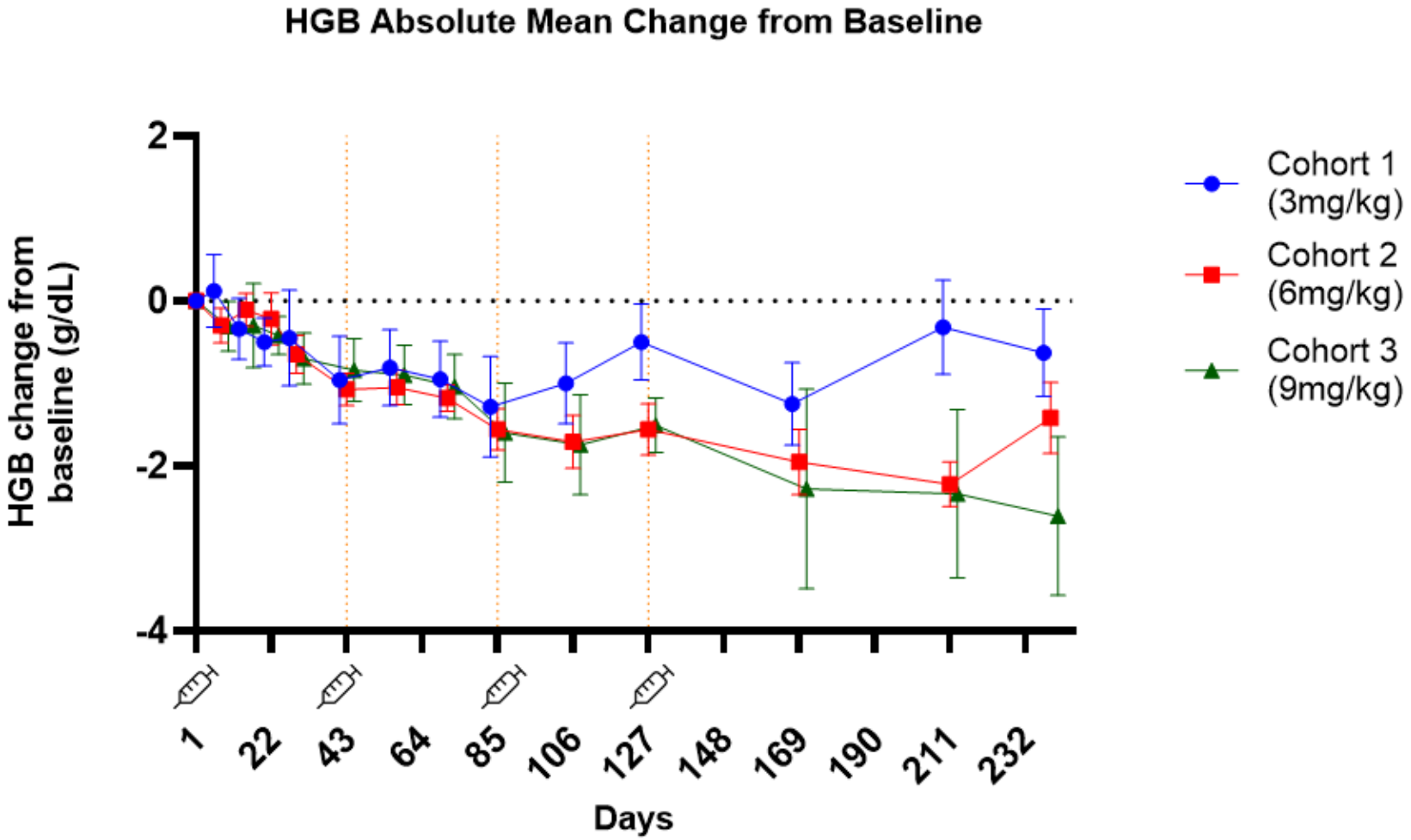
1. Data Presented at the European Hematology Association. June 12, 2025. SANRECO, an On-going Phase 1/2 Study Evaluating Divesiran, Novel GalNAc-conjugated SiRNA, in Patients with Polycythemia Vera. Abstract Code: SS24;
2. Pre-dose from D-201 to D-1, Treatment period D1 to D169 and FU D169 to D239; EoS = End of Study visit; 3. Data cut-off 24th April 2025.

Divesiran Reduced Hematocrit in All PV Patients Regardless of Baseline Levels



1. Data Presented at the European Hematology Association. June 12, 2025. SANRECO, an On-going Phase 1/2 Study Evaluating Divesiran, Novel GalNAc-conjugated SiRNA, in Patients with Polycythemia Vera. Abstract Code: SS24; 2. Orange dotted line represent dosing dates. Error bars represent ± SEM; All data available for each time point is reported; 3. Data cut-off 24th April 2025.

Divesiran Reduced Hemoglobin in All Cohorts



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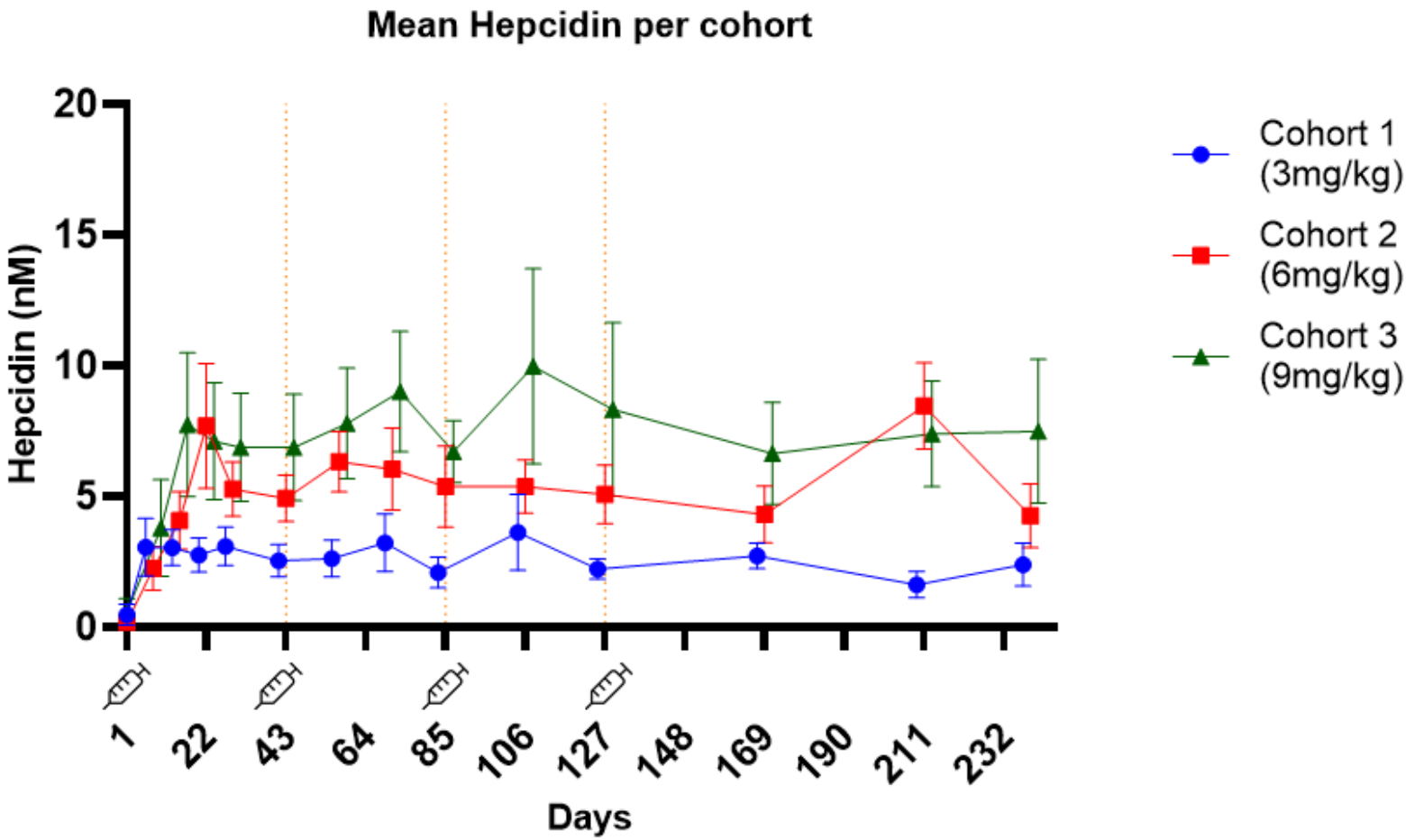
Divesiran Treatment Produced Sustained Increases in Hepcidin



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Divesiran Demonstrated a Favorable Safety and Tolerability Profile

- Divesiran was well tolerated with no dose-limiting toxicities
- No treatment-related serious adverse events or TEAEs leading to discontinuation

Divesiran Phase 1 Study Highlights Potential for First-in-Class siRNA to Address Multiple Unmet Needs in PV

EFFICACY	Divesiran reduced HCT levels and eliminated the need for phlebotomy in target population
DURABILITY	Effects were sustained during the treatment period
SAFETY	Well tolerated with no dose-limiting toxicities
CONVENIENT DOSING	Administered s.c. Q6W

SANRECO Phase 2 Study Overview

Design	• Randomized, double-blind, placebo-controlled study of divesiran in up to 40 PV patients
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 • HCT level <45% prior to dosing
Dosing & Follow-up	• Evaluating Q6W and Q12W dosing regimens • Primary endpoint at 36-weeks
Key Objectives	• Evaluate % of patients with HCT at or below 45% without the need for phlebotomies • Evaluate effect of divesiran in improving PV related symptoms

Study Fully Enrolled – Topline Results Expected in 3Q 2026

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.

Zerlasiran Has Substantial Market Potential

High Cholesterol vs High Lp(a) in Cardiovascular Disease

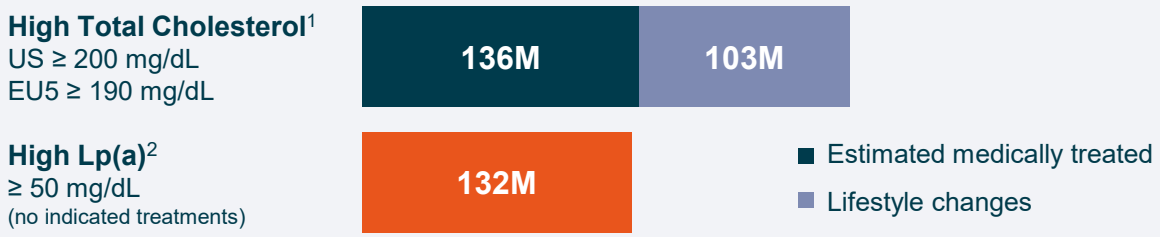
High Cholesterol is a **Modifiable Risk Factor** → Lifestyle changes **can** have a positive impact

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

Zerlasiran Phase 2 Study Supports Competitive Profile with Opportunity to Further Differentiate in Phase 3

EFFICACY	Maximum Lp(a) reductions exceeded 90%
DURABILITY	Lp(a) reductions persisted 60 weeks following first dose
SAFETY	Well tolerated with no major safety issues
CONVENIENT DOSING	Phase 2 study evaluated Q16W and Q24W dosing intervals

1. Journal of the American Medical Association (JAMA). November 18, 2024. Zerlasiran – A Small Interfering RNA-Targeting Lipoprotein(a) A Phase 2 Randomized Clinical Trial | Clinical Pharmacy and Pharmacology | JAMA | JAMA Network.

Zerlasiran Program Status

- ✓ Core Phase 3 readiness activities complete
- ✓ Alignment with global regulatory agencies on Phase 3 design and endpoints

Next Steps:

- Seeking potential third-party partners for Phase 3 development
- First industry CVOT evaluating Lp(a) lowering therapy impact on cardiovascular events scheduled to readout in 2026

Silence is Well Positioned Today with Multiple Potential Value Drivers

Productive GOLD platform, delivering positive results in multiple areas of high unmet need

Multiple clinical programs, including Ph. 3 ready CV asset and Ph. 2 first-in-class siRNA for PV

Extra-hepatic activities demonstrating promising pre-clinical activity

Strong financial position with projected cash runway into 2028

Silencing diseases through precision engineered medicines created with proprietary siRNA technology

Great Place To Work® Certified OKT 2024-OKT 2025 DE

Great Place To Work® Certified OCT 2024-OCT 2025 UK

Great Place To Work® Certified OCT 2024-OCT 2025 USA

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