SILENCE THERAPEUTICS

Silence Therapeutics

January 2023

Forward-Looking Statements

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Silencing diseases through precision engineered medicines created with proprietary siRNA technology

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Evolution of Silence

1998

siRNA work begins in our Berlin research labs

2002

siRNA technology

First core patent application on siRNA technology

2005-2007

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

2009-2015

LNP-siRNA expertise

2016-2021

mRNAi GOLD™

- Focus shifted to GalNAc siRNA expertise
- Robust IP protection activity **(10 technology patent families)**
- Multiple big pharma partnerships
- Nasdaq listing

PRESENT

LIVER

3 programs in the clinic and a rapidly growing pipeline

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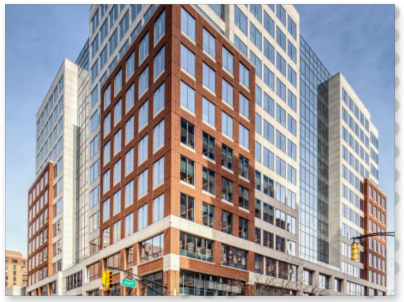
LNP: lipid nanoparticle
siRNA: short interfering RNA

Global Footprint



NEW JERSEY
US OFFICE

LONDON
COMPANY HQ

BERLIN
R&D OPERATIONS

125 EMPLOYEES WORLDWIDE

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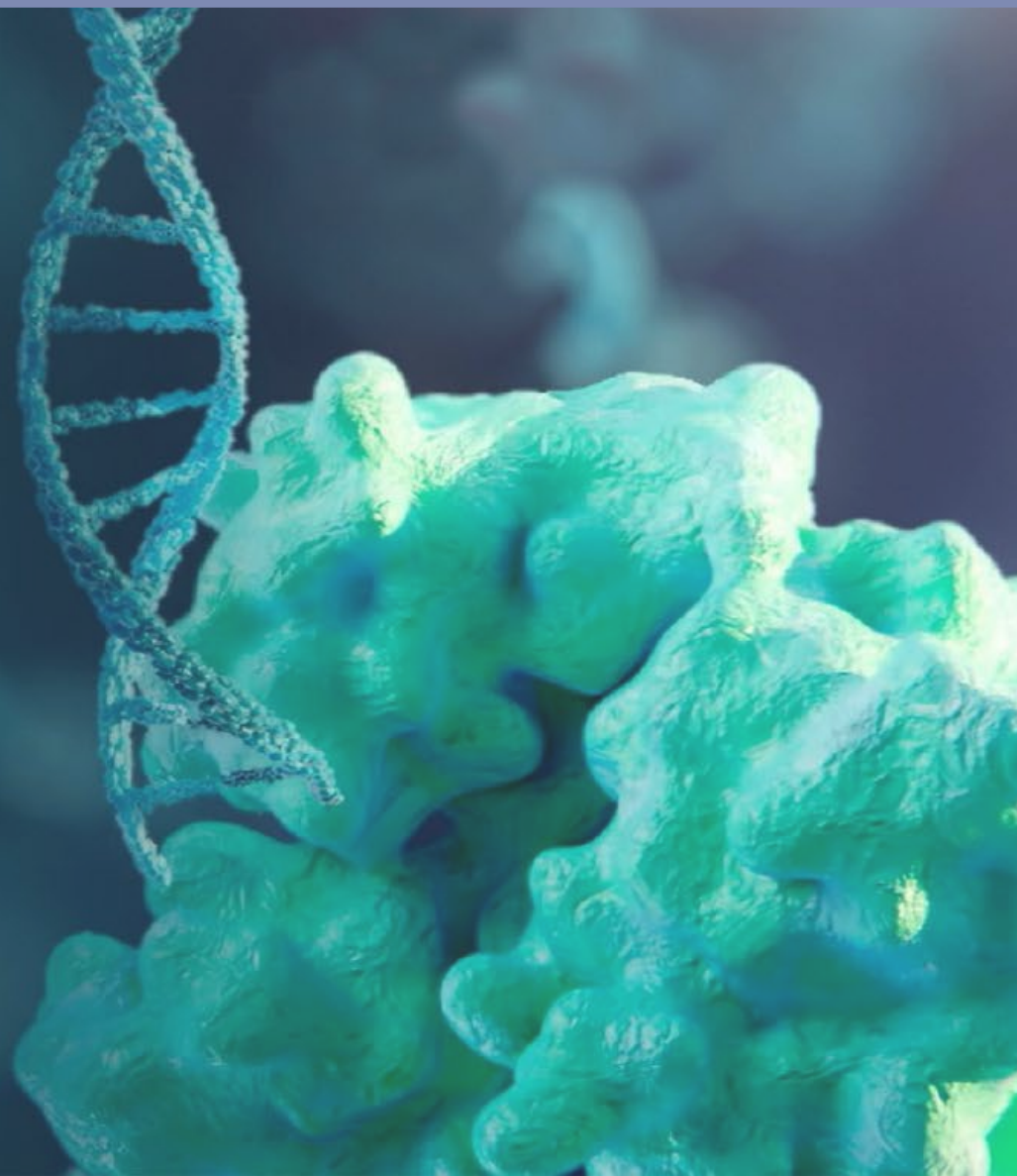
Precision Engineered Medicines to Silence Disease

The Silence siRNA Platform

- **Precision engineered medicines:** 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 genetic diseases
- **Durability, yet Reversibility:** siRNA therapies can achieve long lasting effects after a single dose without permanently altering the gene
- **Pipeline:** advancing multiple wholly owned clinical programs in cardiovascular/rare diseases and +16 partnered programs

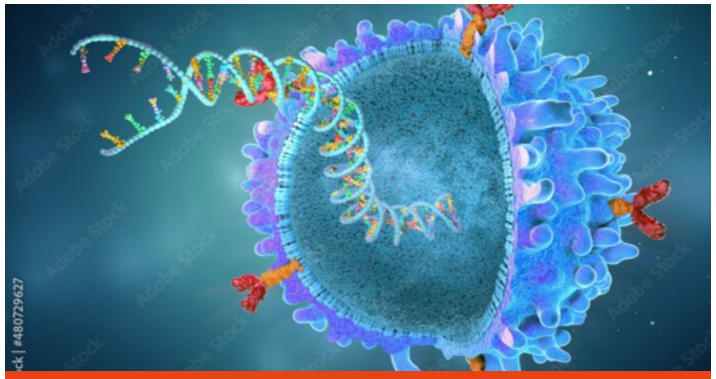


The Difference Between Gene Silencing, Gene Therapy and Gene Editing

Gene Silencing

Prevents expression of a disease-related gene by targeting the mRNA it produces

- ***Precision mechanism:*** Any gene can be silenced by using an siRNA molecule designed to precisely and selectively target the mRNA and induce its cleavage
  - ***Safety profile:*** Precise mRNA targeting and cell-specific delivery reduce potential for side effects
  - ***Reversible:*** Does not alter the DNA
  - ***Treatment modality:*** Requires a few outpatient injections per year



Gene Therapy

Compensates for a disease-related gene by delivering a functional copy of it

- Key benefit: Potential to treat or cure disease in a single dose
- Key limitation: Cannot reduce expression of a disease-related gene

Gene Editing

Corrects a disease-related gene by making additions, changes or deletions to it

- Key benefit: Potential to treat a wider range of diseases in a single dose than gene therapy
- Key limitation: May make unwanted changes to other genes (off-target edits)

- ***Safety profile:*** Not as well established as other modalities, including gene silencing
- ***Non-reversible*:** DNA is permanently altered; side effects may be permanent
- ***Treatment modality:*** Involves major medical procedures

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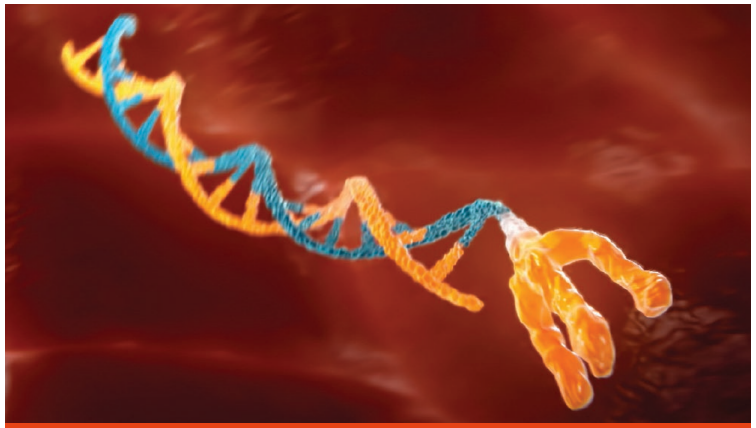
Our Toolbox Considers all Elements of siRNA and Ligand Design

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 mRNAi GOLD™

Hybrid Model

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

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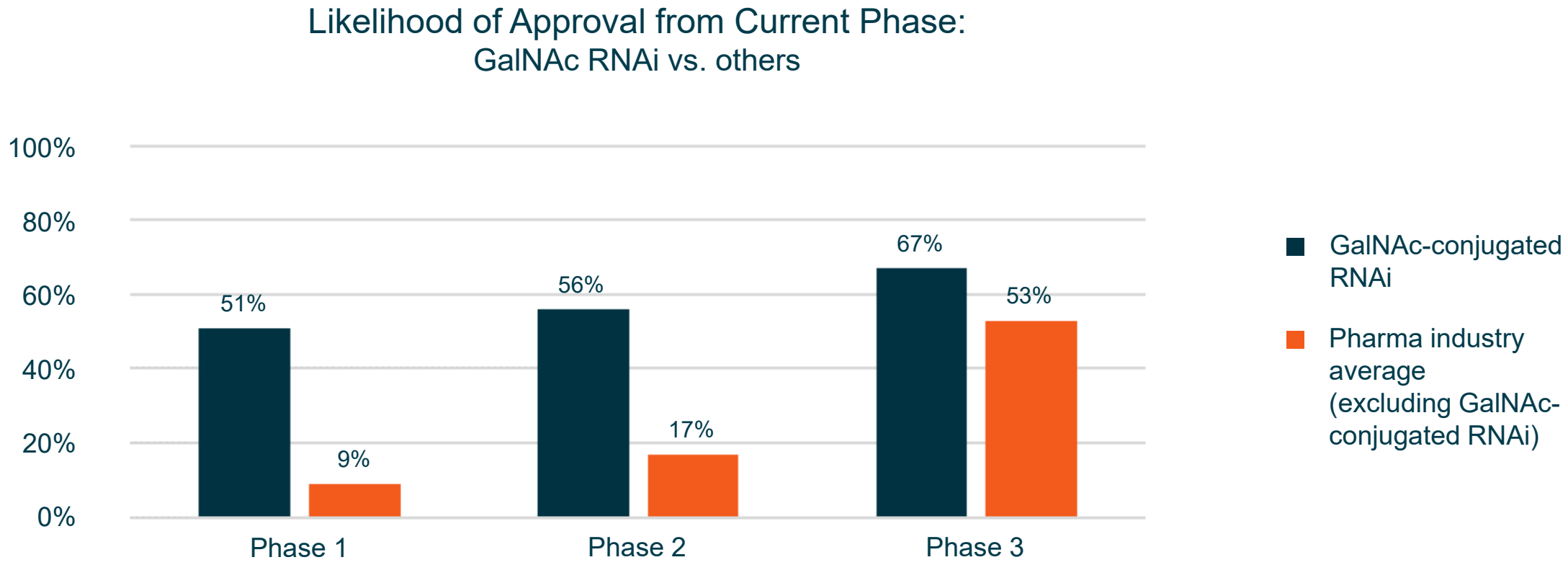
Early-stage GalNAc-conjugated RNAi Programs Have a Much Greater Likelihood of Approval vs. Industry Average



Phase success is defined as the movement of the program to the next phase, not an evaluation of whether endpoints were met.
GalNAc-conjugated RNAi includes both GalNAc-conjugated siRNA and GalNAc-conjugated ASO

Source: Pharmapremia, Informa Pharma Custom Intelligence analysis

Partnership Programs Further Expand Pipeline and Provide ~$7.5 Billion in Potential Milestones Plus Royalties

AstraZeneca

Signed deal to discover, develop and commercialize siRNA therapeutics for cardiovascular, renal, metabolic and respiratory diseases in March 2020

- 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
- AZN to cover preclinical, CMC, clinical development and commercialization costs

Mallinckrodt

Initiated collaboration to develop siRNA therapeutics for complement-mediated diseases in July 2019

- Upfront cash payment of $20 million and an equity investment of $5 million
- Up to $2 billion in potential milestones plus royalties for 3 targets
- Exercised option to license all 3 complement targets

翰森制药
HANSOH PHARMA

Collaboration to develop siRNA therapeutics for undisclosed targets announced in October 2021

- 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 China region rights to those 2 targets
- Hansoh has global rights to a third target

CMC: Chemistry, Manufacturing and Controls

mRNAi GOLD™ Pipeline Balances Proprietary & Partnered Programs

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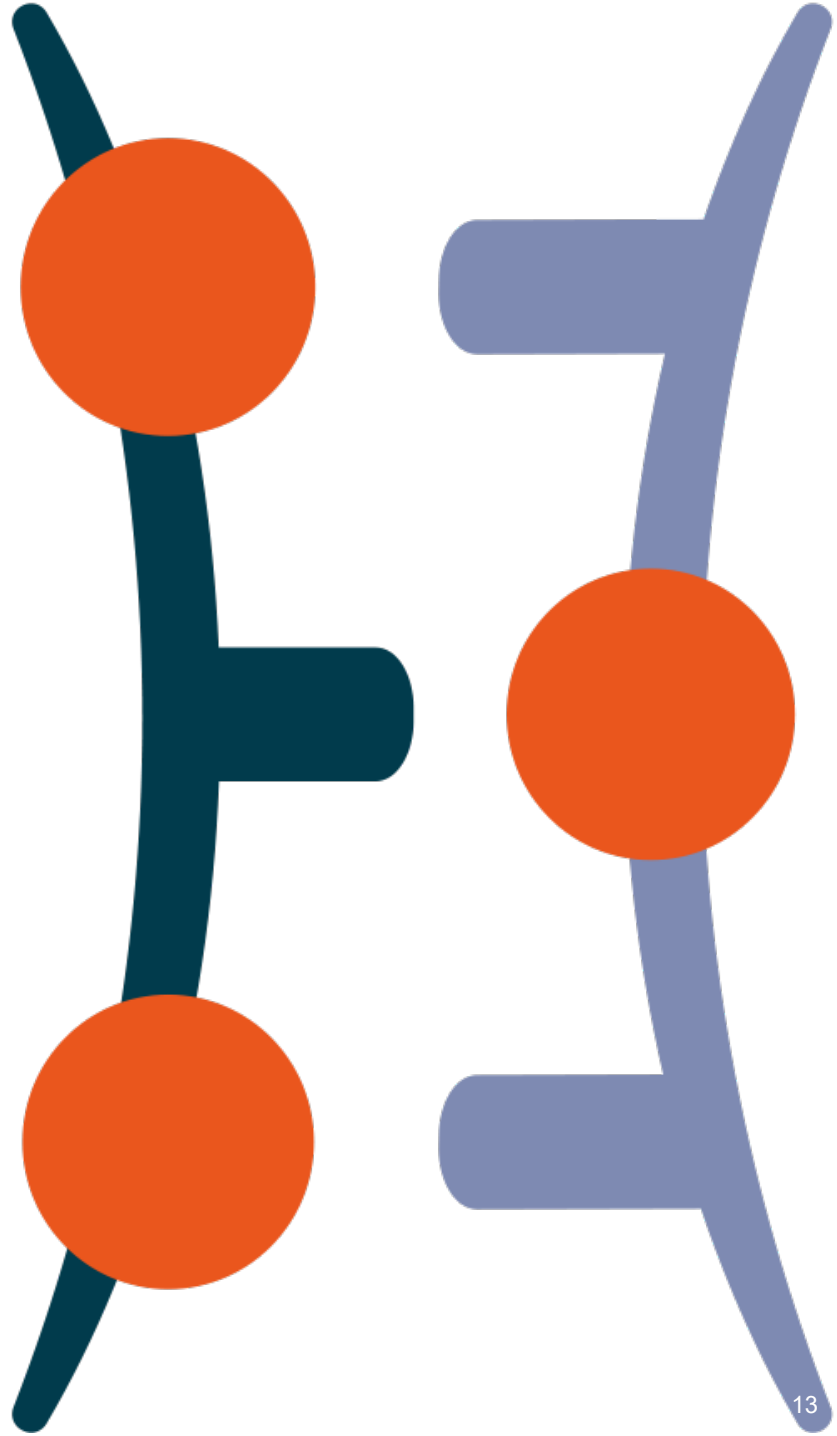
*Silence retains exclusive rights to this program outside of the China region, including Hong Kong, Macau and Taiwan.

Clinical Programs



Positive Clinical Data Shown in Two mRNAi GOLD™ Platform Programs Targeting Common and Rare Diseases

	Target	Ph 1 Study	Efficacy	Durability	Safety / Tolerability
SLN360	*LPA*	32 healthy volunteers with high Lp(a)	Lp(a) reductions observed up to 98% after a single dose	Effects persisting over a five-month period	Well tolerated with no clinically important safety concerns identified
SLN124	*TMPRSS6*	24 healthy volunteers	Average hepcidin increased up to ~4-fold after a single dose (consistent with *TMPRSS6* gene knockdown)	Effects persisting for at least two months (study period)	Well tolerated with no serious or severe treatment emergent adverse events

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SLN360

Cardiovascular Disease

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SLN360 Targets Lp(a): an Independent Risk Factor for Cardiovascular Disease

- Large population worldwide with up to 10% with >90 mg/dL[1] (2-3x increased heart attack risk)[2]
- 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

Targeting Lp(a) with SLN360 Has the Potential to Address Major Unmet Needs in Cardiovascular Disease

Mg/dL: milligrams per deciliter

[1] Varvel et al. Arterioscler Thromb Vasc Biol. 2016;36:2239, Tsimikas et al. Atherosclerosis. 2020;300:1 [2] Kamstrup et al. Circulation. 2008;117:176, Kamstrup et al. JAMA. 2009;301(22):2331

Cardiovascular Event Risk Significantly Increases with High Lp(a)

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

SLN360 Has Substantial Market Potential

High Cholesterol vs High Lp(a) in Cardiovascular Disease

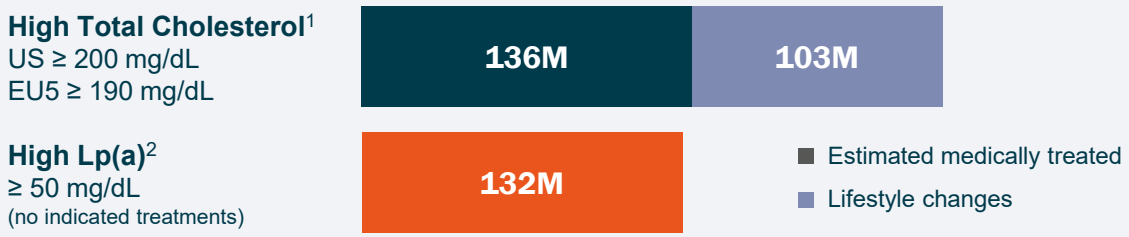
High Cholesterol is a **Modifiable Risk Factor** → Lifestyle changes **can** have a positive impact

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

Growing Awareness of Lp(a) as a Key CV Risk Factor

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

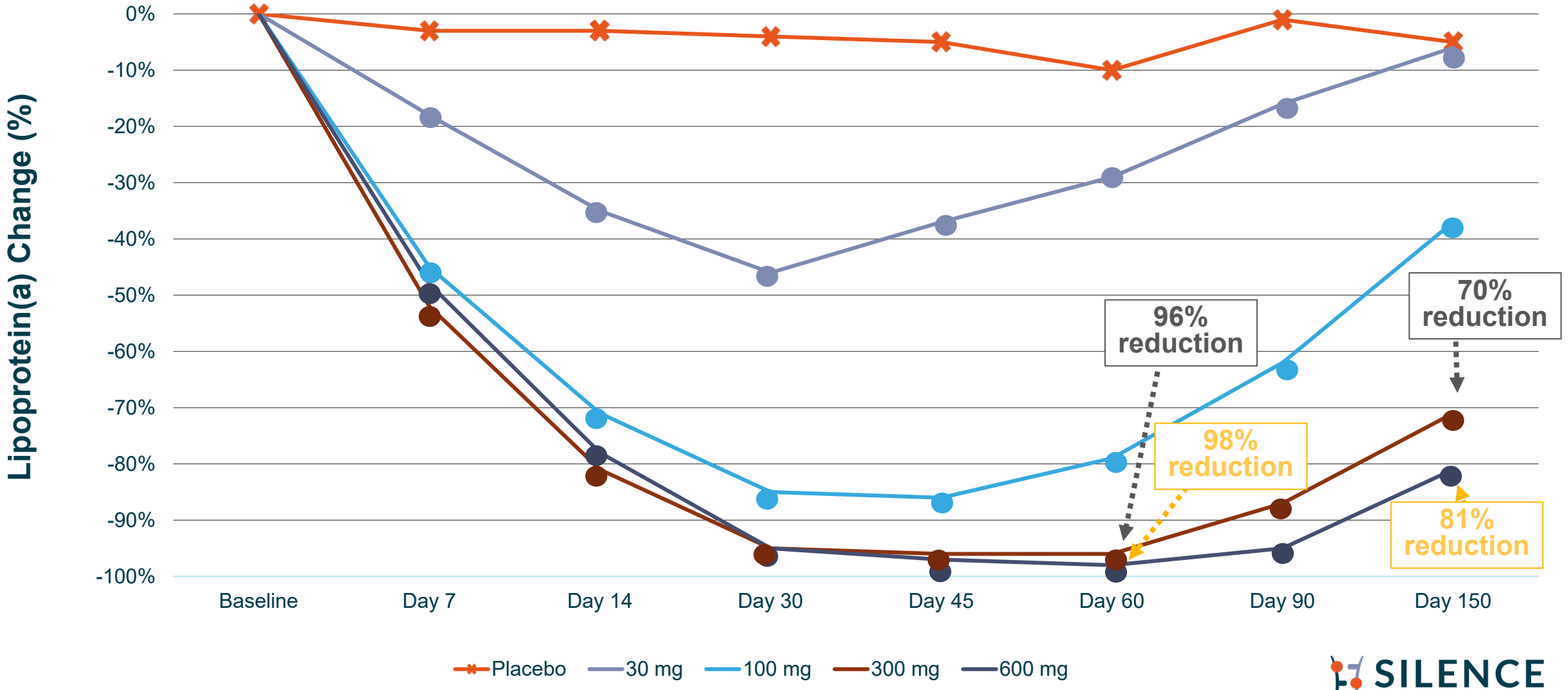
SLN360 Phase 1 Program Overview

Design	Global randomized, double-blind, placebo controlled **single dose** and **multiple dose study**
Aim	Investigate the safety, tolerability, PK and PD response of SLN360 s.c. dosing in subjects with high Lp(a) ≥ 150 nmol/L
Single Dose Arm	• Enrolled 32 healthy adults with high Lp(a) • Evaluated SLN360 30 mg, 100 mg, 300 mg and 600 mg • Reported positive data in February 2022
Multiple Dose Arm	• Enrolling adults with stable ASCVD and high Lp(a) • Evaluating 30 mg, 100 mg, ≥ 300 mg, ≥ 600 mg

nmol/L= nanomoles per liter; PD = Pharmacodynamics; PK = Pharmacokinetics; s.c. = subcutaneous; ASCVD = atherosclerotic cardiovascular disease

https://clinicaltrials.gov/ct2/show/NCT04606602?term=sln360&draw=2&rank=2

SLN360 Lowered Lp(a) Up to 98% After a Single Dose in Phase 1 Study in Healthy Adults with High Lp(a)



Note: Results from the SLN360 APOLLO phase 1 single-ascending dose study in 32 healthy adults with high Lp(a) ≥ 60 mg/dL

Results Simultaneously Presented in a Late Breaker at the ACC Annual Meeting and Published in JAMA in April 2022

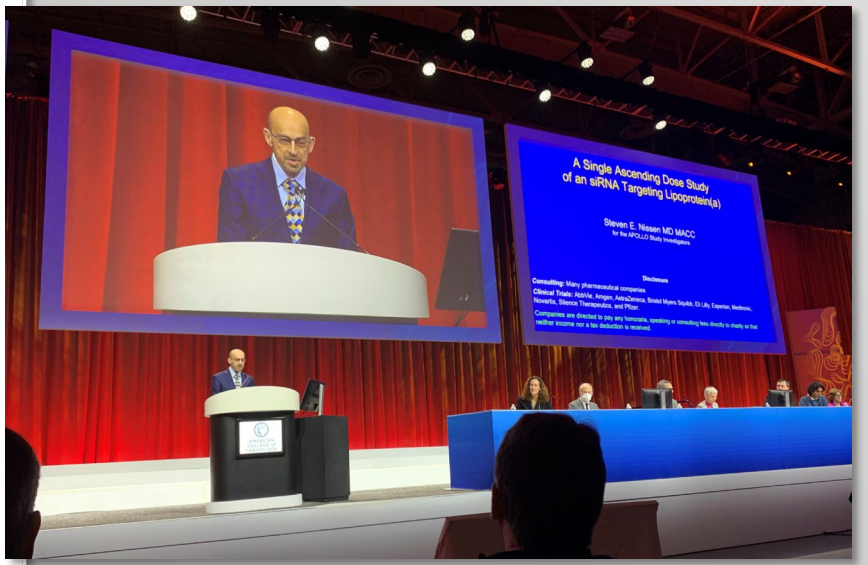
JAMA | Preliminary Communication

Single Ascending Dose Study of a Short Interfering RNA Targeting Lipoprotein(a) Production in Individuals With Elevated Plasma Lipoprotein(a) Levels

Steven E. Nissen, MD; Kathy Wolski, MPH; Craig Balog, BS; Daniel I. Swerdlow, MD, PhD; Alison C. Scrimgeour, MSc; Curtis Rambaran, MD; Rosamund J. Wilson, PhD; Malcom Boyce, MD; Kausik K. Ray, MD; Leslie Cho, MD; Gerald F. Watts, MD, PhD; Michael Koren, MD; Traci Turner, MD; Erik S. Stroes, MD, PhD; Carrie Melgaard, MS; Giles V. Campion, MD, PhD

IMPORTANCE Lipoprotein(a) (Lp[a]) is an important risk factor for atherothrombotic cardiovascular disease and aortic stenosis, for which there are no treatments approved by regulatory authorities.

OBJECTIVES To assess adverse events and tolerability of a short interfering RNA (siRNA) designed to reduce hepatic production of apolipoprotein(a) and to assess associated changes in plasma concentrations of Lp(a) at different doses.



AMERICAN COLLEGE of CARDIOLOGY

ACC22 APRIL 2 - 4 | WASHINGTON, DC

"We thought it would work, but we were surprised by the magnitude and the duration of the effect. Lipoprotein(a) is the last frontier in lipids..."

Steven E. Nissen, M.D., Chief Academic Officer of the Heart, Vascular and Thoracic Institute at Cleveland Clinic

ACC = American College of Cardiology; JAMA = Journal of the American Medical Association

SLN360 Phase 2 Study Overview

Design	Multi-center, randomized, double-blind, placebo-controlled, phase 2 study
Aim	Investigate the efficacy, safety and tolerability of SLN360 s.c. dosing in subjects with high Lp(a) ≥ 125 nmol/L at high risk of ASCVD events
Enrollment	~160 participants
Dosing	2 SLN360 dose levels
Primary Outcome Measure	Time averaged change in Lp(a) from baseline [Week 36]

Lp(a) = lipoprotein(a); s.c. = subcutaneous; nmol/L = nanomoles per liter; ASCVD = atherosclerotic cardiovascular disease

https://clinicaltrials.gov/ct2/show/NCT05537571?term=sln360&draw=2&rank=1

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Anticipated Milestones for SLN360 Program

Phase 1 multiple dose data in patients with high Lp(a) and stable ASCVD	**4Q 2023**
Complete Phase 2 high risk ASCVD study enrollment	**4Q 2023**

SLN124

Hematological Disorders

SLN124 Has Potential for Broad Mechanistic Mode of Action Approach

SLN124 targets *TMPRSS6* and modulates hepcidin – the body's master iron regulator

Positive preclinical data showing therapeutic potential in several hematological disorders

Proof of mechanism demonstrated in healthy volunteer study

DESIGNATIONS

- ✓ Fast track designation for polycythemia vera (PV)
- ✓ Orphan drug designations for PV, beta thalassemia and myelodysplastic syndrome
- ✓ Rare pediatric disease designation for beta thalassemia

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SLN124 Clinical Programs

Iron Loading Anemias (Beta Thalassemia)

Prevalence
1/100,000[1,2,3]


~5,000


~100,000

- Globin gene mutations interfere with red blood cell production and cause anemia
- The majority are dependent on regular blood transfusions (TDT), while others are transfused less frequently (NTDT)
- Severe limitations and low quality of life with current treatments
- Opportunity to improve quality of life by reducing the frequency of blood transfusions
- Burdens include severe anemia, transfusion dependence, toxic iron overload

Polycythemia Vera (PV)

Prevalence
44-57/100,000[4]


~150,000*


~3.5m*

- Genetic mutations cause overproduction of red blood cells, white blood cells and platelets
- High hematocrit increases blood viscosity and contribute to **elevated thrombotic risk**
- Patients with **hematocrit between 45-50% are ~4x more likely to die** from CV causes or major thrombotic events than those < 45%[5]
- Most patients with PV are **iron deficient at diagnosis – repeated phlebotomy exacerbates this**
- Primary treatment goal is to maintain hematocrit < 45%

*Using 44/100,000
Global population: 7,800m

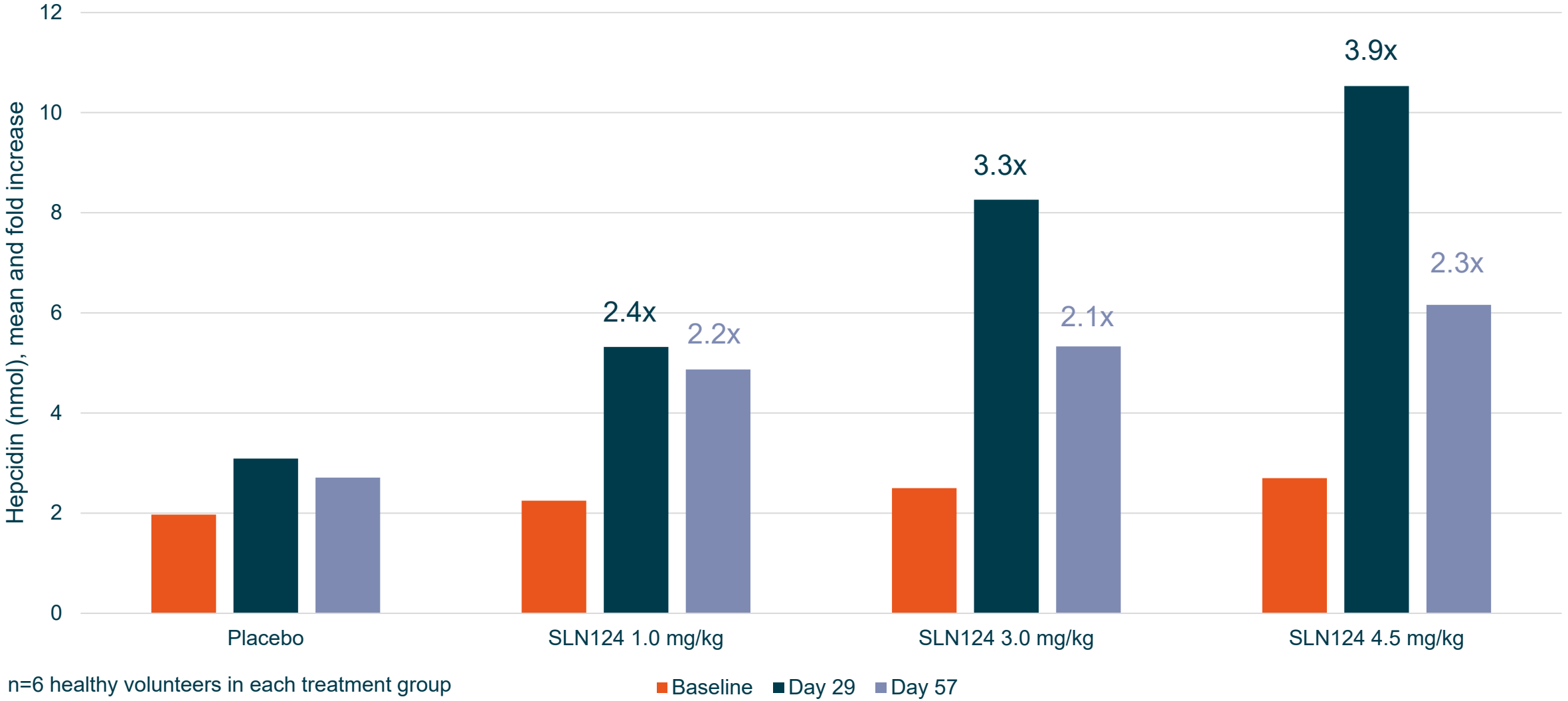
[1] Mehta, J. et al. Leukemia & Lymphoma (2014); [2] Marchioli, R. et al., NEJM 2013,368;22-33; [3] Galanello, R., Origa, R. Orphanet J Rare Dis (2010); [4] Kattamis, A. et al. Eur J Haematol (2020); [5] Modell, B., Darlison, M., Bull World Health Organ (2008);

SLN124 Proof of Mechanism Established in Healthy Volunteer Study

EFFICACY	SLN124 increased average hepcidin up to ~4-fold and reduced serum iron ~50% after a single dose
DURABILITY	Activity persisted for at least 2 months (study period)
SAFETY	Well tolerated with no serious or severe treatment emergent adverse events

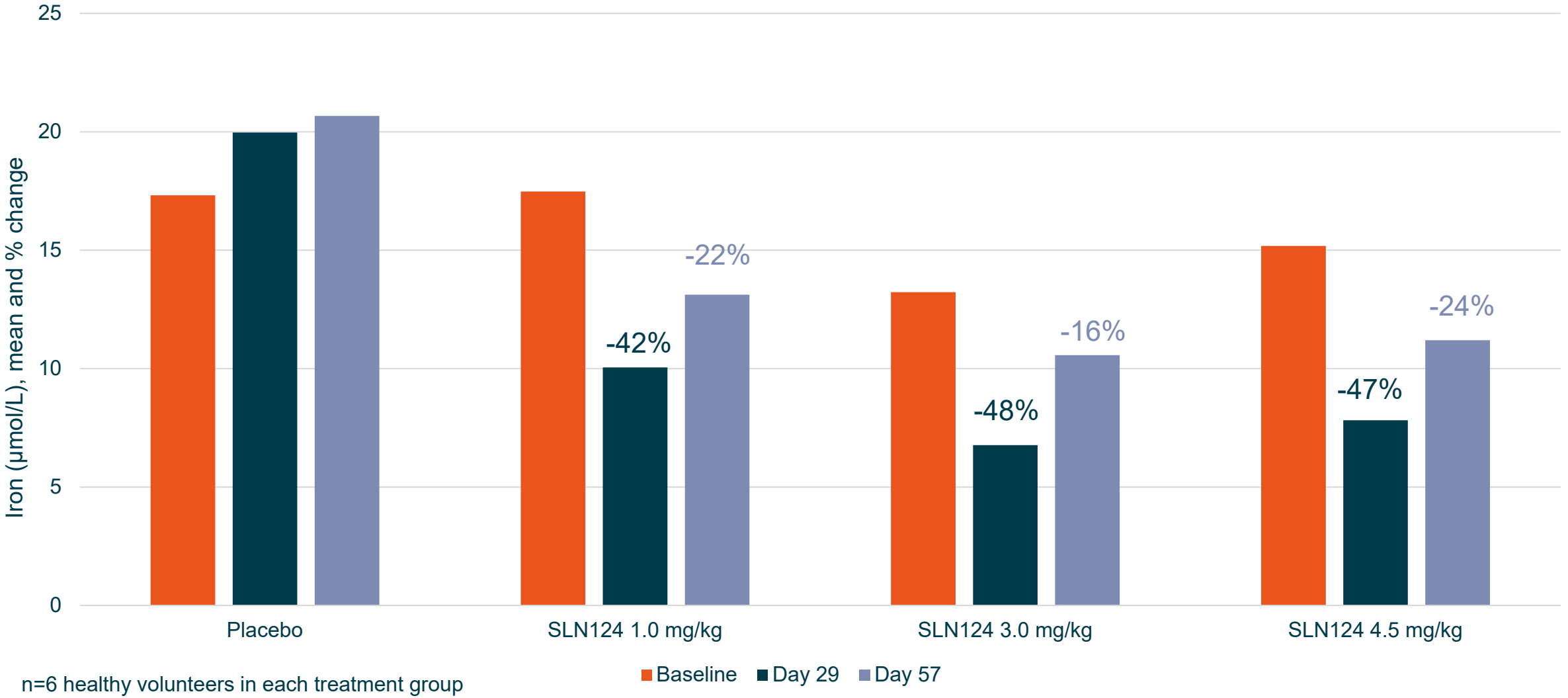
Data presented at ASH 2021

SLN124 Increased Average Hepcidin up to ~4-Fold After a Single Dose with Activity Sustained for ≥ 2 Months



n=6 healthy volunteers in each treatment group

SLN124 Reduced Serum Iron by ~50% After a Single Dose with Activity Sustained for ≥ 2 Months



n=6 healthy volunteers in each treatment group

SLN124 Phase 1 Program in Adult Thalassemia

Design	Global, randomized, single-blind, placebo-controlled **single dose** and **multiple dose study**
Aim	Investigate the safety, tolerability, PK and PD response of SLN124 s.c. dosing in adults with NTD thalassemia
Enrollment	~ 24 adults with NTD thalassemia
Dosing	1 mg/kg, 3 mg/kg and 6 mg/kg
Primary Outcome Measures	Incidence of treatment-emergent adverse events [Day 86 and Day 140] PK and PD data will be reported in multiple dose portion

PK = Pharmacokinetics; PD = Pharmacodynamics; s.c. = subcutaneous; NTD = non-transfusion dependent; mg/kg = milligrams per kilogram

https://clinicaltrials.gov/ct2/show/NCT04718844?term=sln124&draw=2&rank=3

Preliminary Single Dose Results from SLN124 Phase 1 Study in Thalassemia Patients

- No serious adverse events, no severe TEAEs that were SLN124 related
- No TEAEs leading to withdrawal
- No dose limiting toxicities or drug related liver injury were observed

- Effects on hepcidin, serum iron, transferrin saturation and hemoglobin are being evaluated in ongoing multiple dose arm

Multiple dose data expected in 4Q 2023

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TEAEs = treatment emergent adverse events

SLN124 Phase 1/2 Study in Polycythemia Vera (PV)

Design	**Phase 1** is an open-label, dose-finding study **Phase 2** is a randomized, double-blind, placebo-controlled study
Aim	Assess the safety, tolerability, efficacy, PK, and PD response of SLN124 s.c. dosing in patients with PV
Enrollment	Up to 65 participants total
Primary Outcome Measures	**Phase 1:** Incidence of treatment-emergent adverse events and assessment of the number of phlebotomies at intervals **Phase 2:** Number of patients who are phlebotomy free after treatment

PD = Pharmacodynamics; PK = Pharmacokinetics; s.c. = subcutaneous
https://clinicaltrials.gov/ct2/show/NCT05499013?term=sln124&draw=2&rank=1

Financial Highlights

SLN: Nasdaq	
Stock Price (1/4/23)	$15.41 per ADS
Common Shares Outstanding (9/30/22)	~35,893,337 ADS
Market Capitalization (1/4/23)	~$553m
Cash (9/30/22)	~$113m
Debt	$0

Note: ADS each represent 3 ordinary shares nominal value

Key Investment Highlights

- Wholly owned SLN360 program targeting large cardiovascular indication with high unmet need
  - *Phase 2 ASCVD study now underway*
- Second wholly owned SLN124 program has shown potential in multiple hematological diseases
  - *PV study open for enrollment*
- Partnered pipeline represent up to 16 additional programs and ~$7.5B in potential milestones plus royalties
- Technology platform with broad utility – clinical proof of concept established in both rare and common diseases
- Solid financial position - hybrid business model provides potential source for non-dilutive capital

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Silencing diseases through precision engineered medicines created with proprietary siRNA technology
Great Place To Work. Certified OCT 2022-OCT 2023 UK
Great Place To Work. Certified NOV 2022-NOV 2023 DE
Great Place To Work. Certified OCT 2022-OCT 2023 USA
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