Silence Therapeutics

November 16, 2022

Forward-Looking Statements

The information contained in this presentation is being supplied and communicated to you solely for your information and may not be reproduced, further distributed to any other person or published, in whole or in part, for any purpose.

The distribution of this presentation in certain jurisdictions may be restricted by law, and persons into whose possession this presentation comes should inform themselves about, and observe, any such restrictions. Although reasonable care has been taken to ensure that the facts stated in this presentation are accurate and that the opinions expressed are fair and reasonable, the contents of this presentation have not been verified by Silence Therapeutics plc (the "Company") or any other person. Accordingly no representation or warranty, express or implied, is made as to the fairness, accuracy, completeness or correctness of the information and opinions contained in this presentation and no reliance should be placed on such information or opinions. None of the Company, or any of its respective members, directors, officers or employees nor any other person accepts any liability whatsoever for any loss howsoever arising from any use of such information or opinions or otherwise arising in connection with this presentation. No part of this presentation, or the fact of its distribution, should form the basis of or be relied upon in connection with any contract or commitment or investment decision whatsoever. This presentation does not form part of any offer of securities, or constitute a solicitation of any offer to purchase or subscribe for securities or an inducement to enter into any investment activity. Recipients of this presentation are not to construe its contents, or any prior or subsequent communications from or with the Company or its representatives as investment, legal or tax advice. In addition, this presentation does not purport to be all-inclusive or to contain all of the information that may be required to make a full analysis of any transaction. Further, the information in this presentation is not complete and may be changed. Recipients of this presentation should each make their own independent evaluation of the information and of the relevance and adequacy of the information in this document and should make such other investigations as they deem necessary.

This presentation may contain forward-looking statements that reflect the Company's current views and expectations regarding future events. In particular certain statements with regard to management's strategic vision, aims and objectives, the conduct of clinical trials, the filing dates for product license applications and the anticipated launch of specified products in various markets, the Company's ability to find partners for the development and commercialisation of its products as well as the terms for such partnerships, anticipated levels of demand for the Company's products (including in development), the effect of competition, anticipated efficiencies, trends in results of operations, margins, the market and exchange rates, are all forward looking in nature.

Forward-looking statements involve risks and uncertainties that could cause actual results to differ materially from those expressed or implied by the forward looking statements. Although not exhaustive, the following factors could cause actual results to differ materially from those the Company expects: difficulties inherent in the discovery and development of new products and the design and implementation of pre-clinical and clinical studies, trials and investigations, delays in and results from such studies, trials and investigations that are inconsistent with previous results and the Company's expectations, the failure to obtain and maintain required regulatory approvals, product and pricing initiatives by the Company's competitors, inability of the Company to market existing products effectively and the failure of the Company to agree beneficial terms with potential partners for any of its products or the failure of the Company's existing partners to perform their obligations, the ability of the Company to obtain additional financing for its operations and the market conditions affecting the availability and terms of such financing, the successful integration of completed mergers and acquisitions and achievement of expected synergies from such transactions, and the ability of the Company to identify and consummate suitable strategic and business combination transactions and the risks described in our most recent Admission Document.

By participating in this presentation and/or accepting any copies hereof you agree to be bound by the foregoing restrictions and the other terms of this disclaimer.

Silence VISION and STRATEGY

VISION

Transform peoples' lives around the world by **silencing diseases** through our **precision** engineered **medicines** and driving positive change for the communities around us.

STRATEGY

Maximize our proprietary **mRNAi GOLD™** platform through **hybrid business model**

Geographic Operations

SILENCE THERAPEUTICS

Silence is a Leader in siRNA Poised for Transformation

Pioneers in RNAi	• Two decades of know-how combined with robust and growing IP estate • Global footprint – HQ in London, R&D in Berlin and Hoboken, NJ office
Advancing Clinical Programs	• SLN360 (Cardiovascular Disease) - positive data in phase 1 study in healthy volunteers with high Lp(a)[1] • SLN124 (Hematological Disorders) – proof of concept in healthy volunteers; safety data in thalassemia • SLN501 (Complement Mediated Diseases) - phase 1 study with Mallinckrodt underway
Proprietary mRNAi GOLD™ Platform	• Clinical proof of concept established in two wholly owned programs • Partnered pipeline represents up to 16 programs and ~$7.5B in potential milestones plus royalties • Leveraging hybrid business model to maximize substantial platform opportunity
Strong Financial Position	• Hybrid business model provides potential source for non-dilutive capital[2] • Cash ~$113m as of September 30, 2022 • Nasdaq listed (SLN) - market cap ~$500m[3]

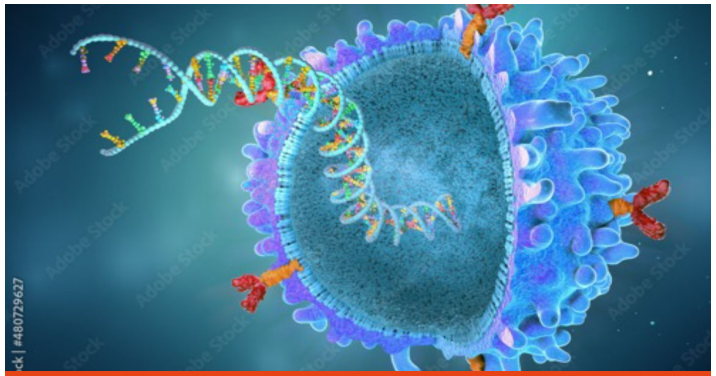
1 Lp(a) = Lipoprotein(a)
2 Hybrid business model defined as leveraging both wholly owned and partnered programs to advance mRNAi GOLD™ pipeline
3 Market Capitalization as of November 14, 2022

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
  - ***Permanence:*** Reversible by reducing dose or pausing treatment; 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

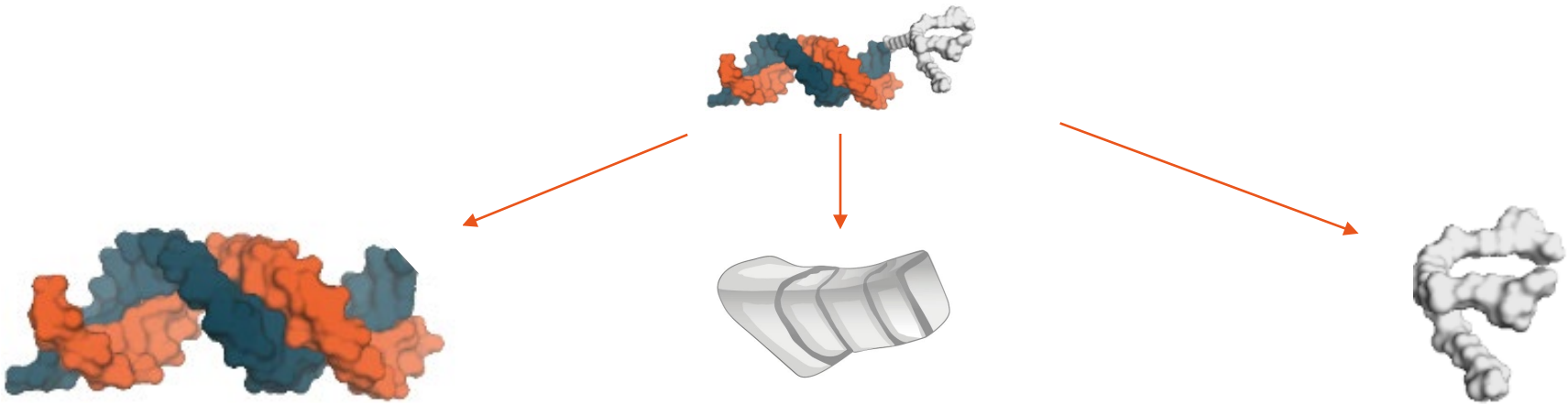
- Key benefit: Potential to treat or cure disease in a single dose
- Key limitation: Cannot reduce expression of a disease-related gene
  - ***Safety profile:*** Not as well established as other modalities, including gene silencing
  - ***Permanence:*** Non-reversible; DNA is permanently altered; side effects may be permanent
  - ***Treatment modality:*** Involves major medical procedures

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)

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

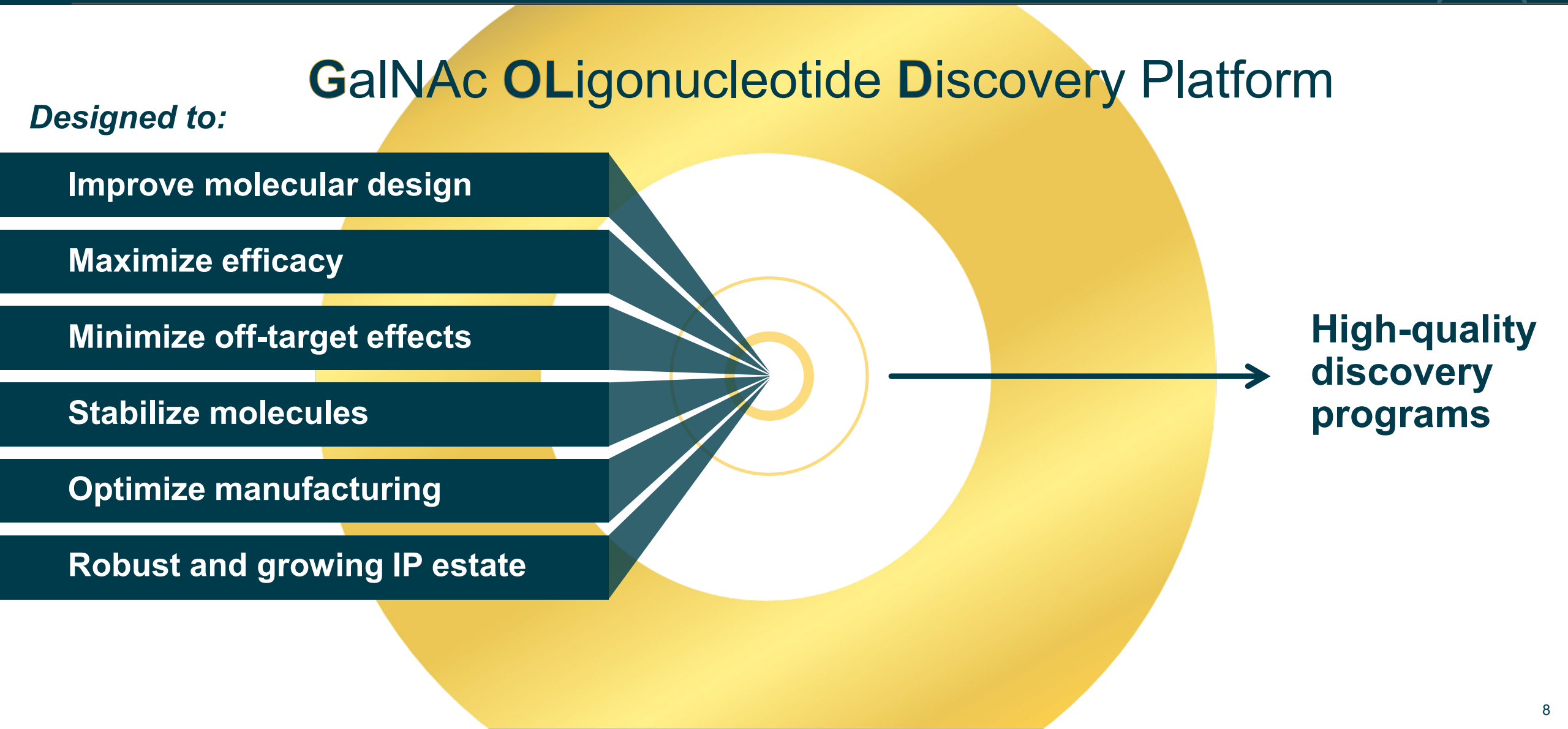
Continuous Fine-Tuning to Further Improve Performance

mRNAi GOLD™ Platform Approach: Precision-Engineered Therapies

GalNAc OLigonucleotide Discovery Platform

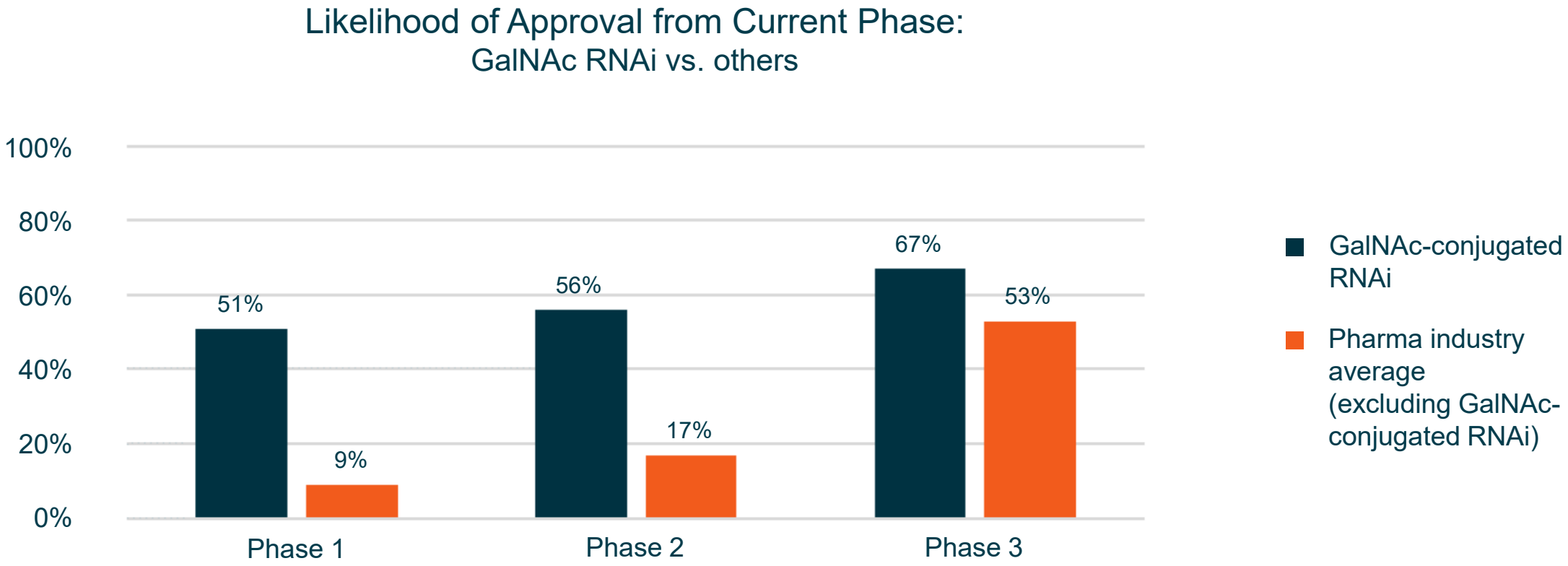
Designed to:

- Improve molecular design
- Maximize efficacy
- Minimize off-target effects
- Stabilize molecules
- Optimize manufacturing
- Robust and growing IP estate



High-quality discovery programs

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

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

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

Collaboration to develop siRNA therapeutics for undisclosed targets announced in Oct. 2021

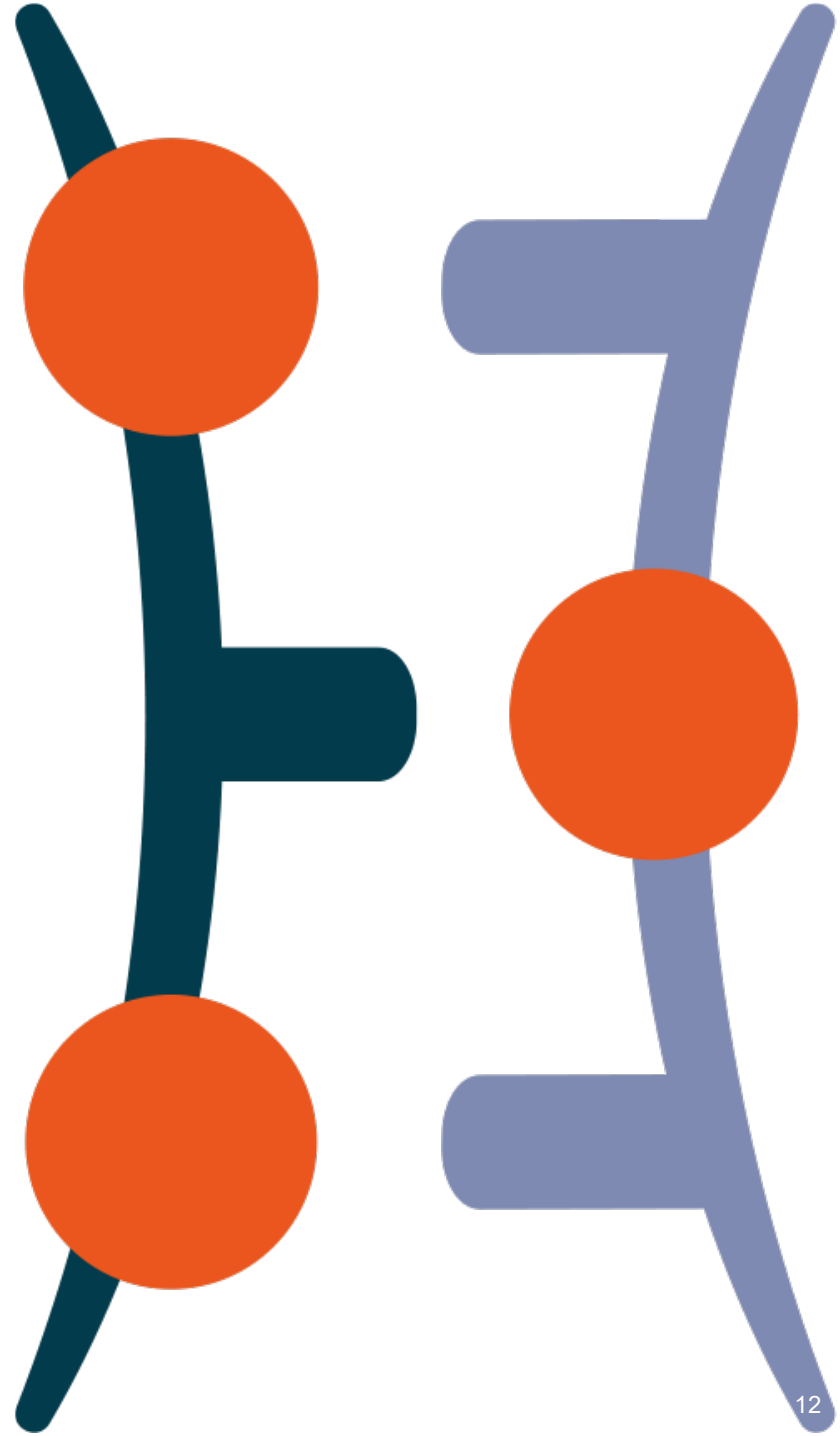
- Upfront cash payment of $16 million and up to $1.3 billion in potential milestones plus royalties
- Silence has exclusive rights to 2 targets in all territories except China region; Hansoh has China region rights to those 2 targets
- Hansoh has global rights to a third target

CMC: Chemistry, Manufacturing and Controls

Pipeline Balances Proprietary & Partnered Programs

*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* gene	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* gene	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

SLN360

Cardiovascular Disease

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

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

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

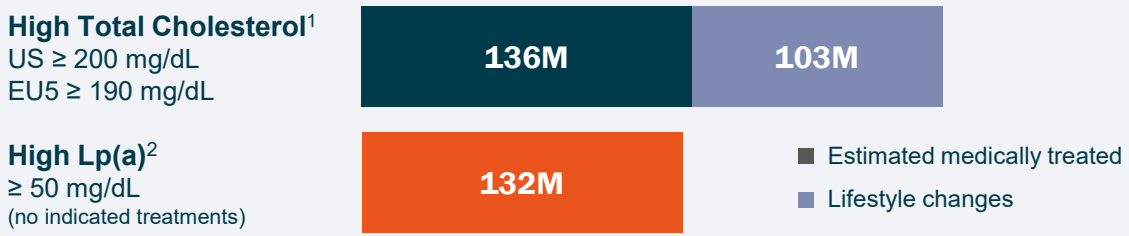
High Cholesterol is a **Modifiable Risk Factor** → Lifestyle changes **can** have a positive impact

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)

CCS recommends 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

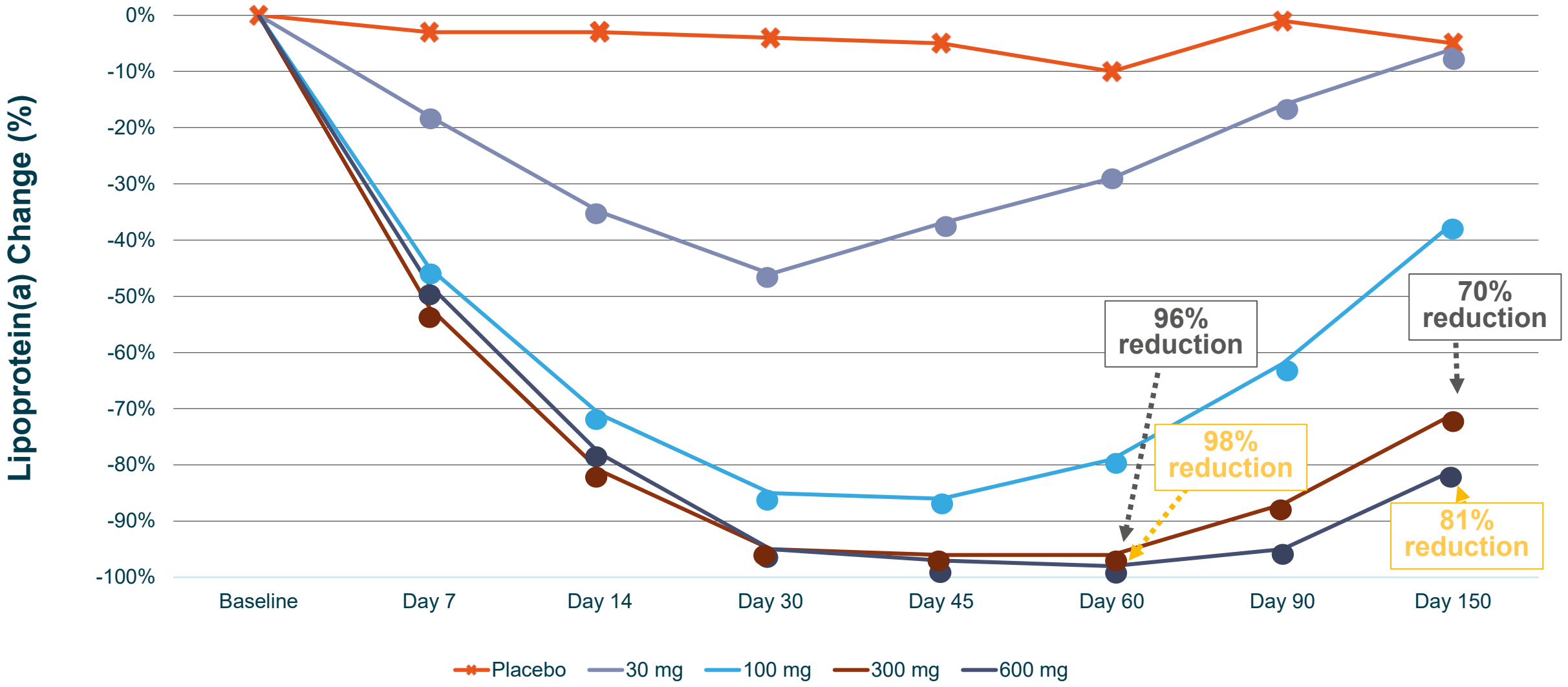
SLN360 Phase 1 Program Overview

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

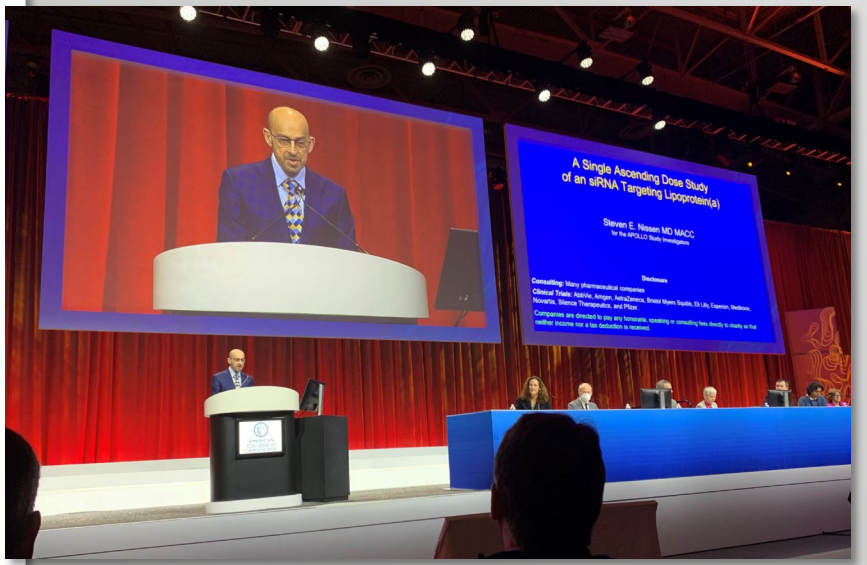
JAMA | Preliminary Communication

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	3 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

SLN124

Hematological Disorders

SLN124 Has Potential for Broad Mechanistic Mode of Action Approach

SLN124 targets *TMPRSS6* and controls 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

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

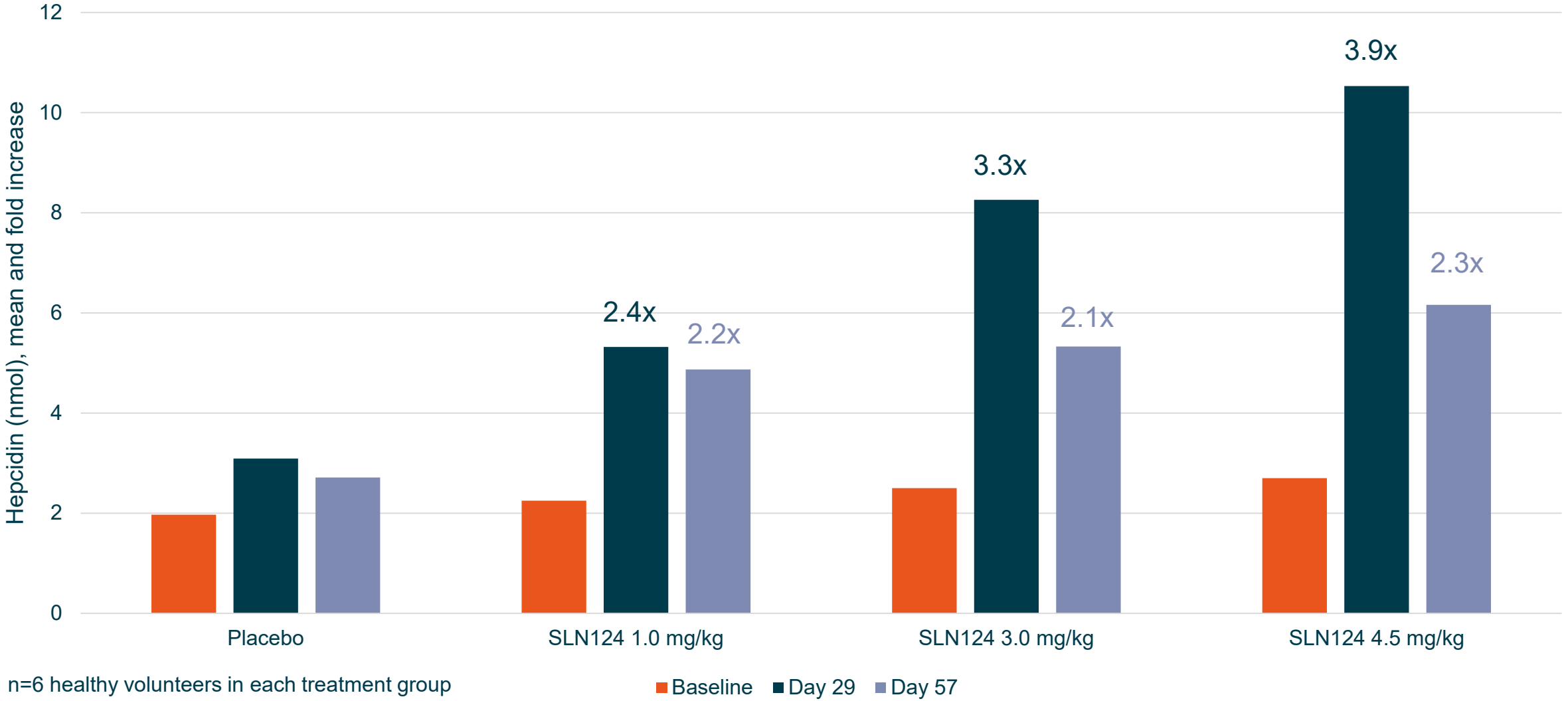
[1] Mehta, J. et al. Leukemia & Lymphoma (2014); [2] Marchioli, R. et al., NEJM 2013,368;22-33; [3] Galanello, R., Origa, R. Orphanet J Rare Dis (2010); [4] Kattamis, A. et al. Eur J Haematol (2020); [5] Modell, B., Darlison, M., Bull World Health Organ (2008);

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

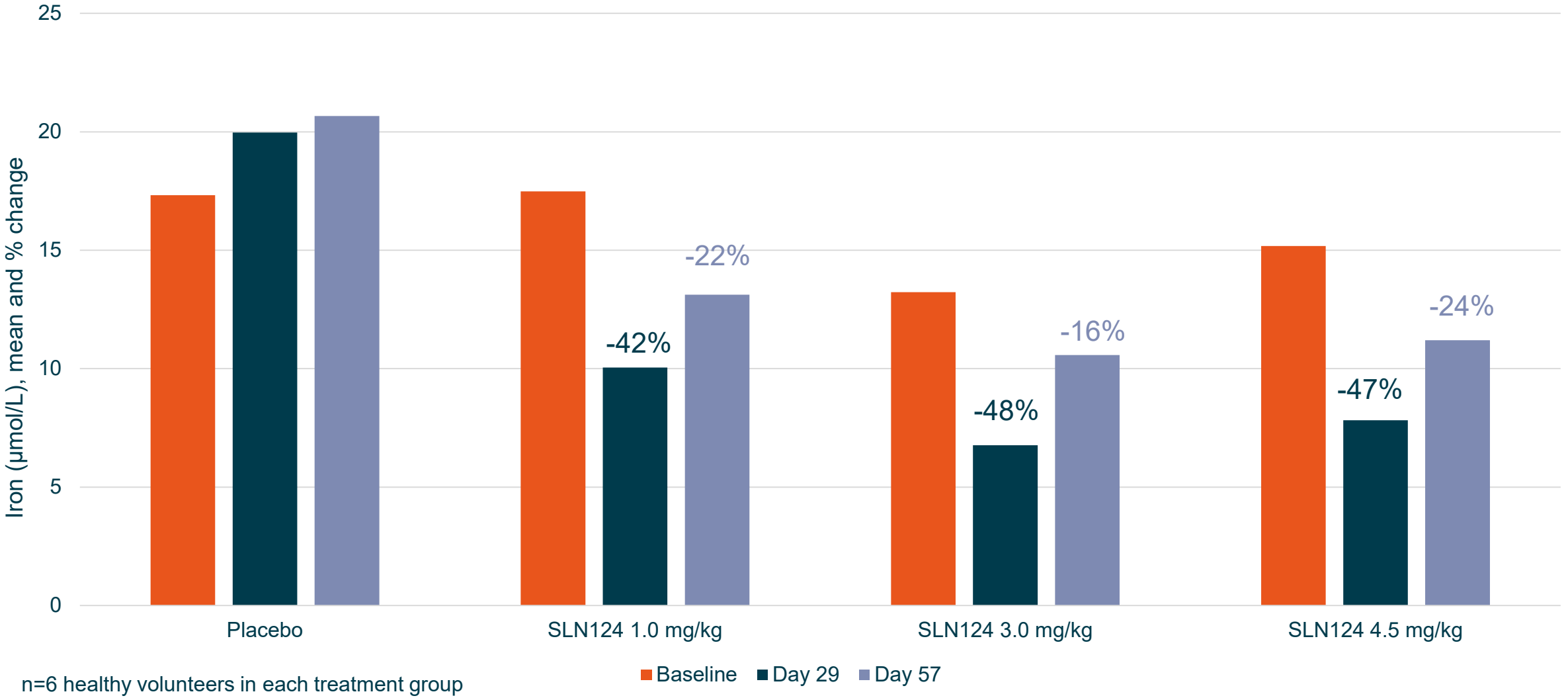
Data presented at ASH 2021

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

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	~ 65 participants
Primary Outcome Measures	Incidence of treatment-emergent adverse events Assessment of the number of phlebotomies at intervals

PD = Pharmacodynamics; PK = Pharmacokinetics; s.c. = subcutaneous

https://clinicaltrials.gov/ct2/show/NCT05499013?term=sln124&draw=2&rank=1

Maximizing Output through the Silence mRNAi GOLD™ Platform

High-quality target identification using translational genomics

Lower attrition rates in discovery enabled by machine learning

GalNAc strategic partnerships to enhance pipeline opportunities

Financial Highlights

SLN: Nasdaq	
Stock Price (11/14/22)	$ 13.89 per ADS
Common Shares Outstanding (9/30/22)	~35,893,337 ADS
Market Capitalization (11/14/22)	~$500m
Cash (9/30/22)	~$113m
Debt	$0

Note: ADS each represent 3 ordinary shares nominal value

Key Potential Value Drivers

- Wholly owned SLN360 program targeting large cardiovascular indication with high unmet need – *on-track to start phase 2 study by year end*
- Second wholly owned SLN124 program has shown potential in multiple rare hematological diseases – *on-track to start phase 1/2 PV study by year end*
- Partnered pipeline represent up to 16 additional programs and ~$7.5B in potential milestones plus royalties
- Solid financial position following August financing - hybrid business model provides potential source for non-dilutive capital