SILENCE THERAPEUTICS

Silence Therapeutics

July 13, 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



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



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

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) • **SLN124 (Hematological Disorders)** – positive data in phase 1 study in healthy volunteers • **SLN501 (Complement Mediated Diseases)** – phase 1 study with Mallinckrodt underway
Proprietary mRNAi GOLD™ Platform	• **Positive clinical data in two programs showed robust knockdown of target gene, strong durability after a single dose and excellent safety profiles** • **Leveraging hybrid business model to maximize substantial opportunity in the liver**
Strong Financial Position	• **~$74m / £59m at the end of March 2022** • **$5 million in collaboration milestones to be received in Q2'22** • **Nasdaq listed (SLN) - market cap ~$335m***

* Market Capitalization as of July 8, 2022

Lp(a) = Lipoprotein(a)

Executive Leadership Team with Deep Sector Experience



Craig Tooman

President and CEO

- 30+ years of experience in the biopharmaceutical industry
- Previously CEO at Aratana Therapeutics where he successfully negotiated a merger with Elanco
- Former CFO of Enzon Pharma until its acquisition by Sigma Tau, and prior to that he led $1.1B M&A initiative of ILEX Oncology and Genzyme Corporation



Rhonda Hellums

Chief Financial Officer

- 25+ years of experience in corporate finance, accounting, strategic planning, mergers and acquisitions, treasury management, investor and public relations
- Held management positions at KCI (now 3M+KCI), Genzyme and Ilex Oncology
- Previously CFO at Deer Oaks Mental Health and Aratana Therapeutics



Dr. Barbara Ruskin

SVP, General Counsel and CPO

- 25+ years of global experience in life science IP and corporate law
- Former Partner at Ropes and Gray, associate at Fish & Neave, and SVP GC / CPO at biopharma companies
- Managed general legal and IP matters related to financing and regulatory, BD, licensing and patent portfolio management



Dr. Giles Campion

EVP, Head of R&D and CMO

- 30+ years of experience in the biopharmaceutical industry
- Former CMO and SVP R&D at Prosensa, playing a major role in their Nasdaq IPO and subsequent sale to Biomarin for $680m
- Most recently CMO at Albumedix and held senior R&D roles at GE Healthcare, Novartis and SmithKline Beecham prior
- Medical degree and doctorate from Bristol University



Dr. Marie Wikström Lindholm

SVP, Molecular Design

- 13+ years' experience with oligonucleotide therapeutics
- Former Expert Scientist in Discovery Technology and Head of Targeted Delivery at Santaris Pharma / Roche
- Authored 60+ patent applications and peer-reviewed scientific publications



Jorgen Wittendorff

SVP, Head of Manufacturing

- 25+ years experience in pharmaceutical development
- Extensive experience in complex manufacturing and regulatory compliance (FDA, EMA, and PMDA)
- Held senior CMC and Supply roles at Ablynx and Ferring Pharmaceuticals

siRNA Can Inhibit Expression of Disease-Associated Genes

nucleus

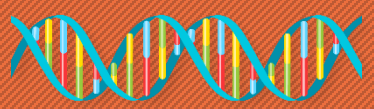
cytoplasm

HEALTHY

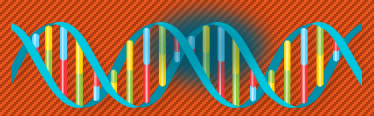
Genes encode messages for all features in the body

DISEASE

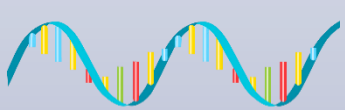
In certain diseases the DNA is mutated or abnormally expressed



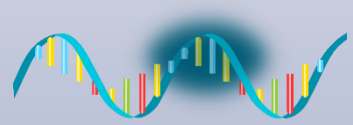
DNA



The information in DNA is transcribed into messenger RNA (mRNA)

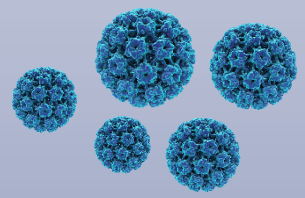


mRNA

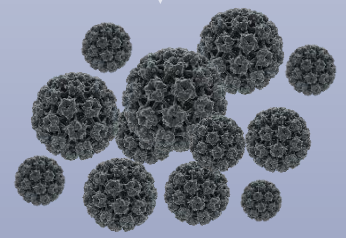


Abnormal DNA message is carried into resulting mRNA

mRNA is then made into proteins. Proteins are responsible for most functions in the body

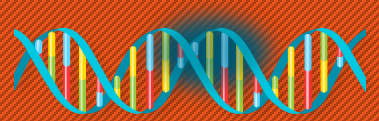


protein



In some cases mutations instruct the cell to produce too much protein or the protein made does not work

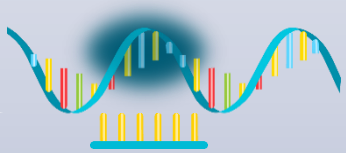
siRNA Can Precisely Target and Silence Disease-Associated Genes



Mutated DNA

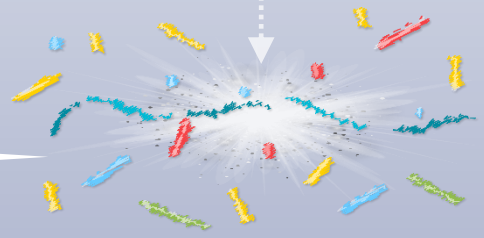
SILENCE THERAPEUTICS

Target-specific short interfering RNA (siRNA) binds to the mRNA

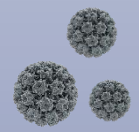


mRNA

mRNA is degraded and gene is “silenced”



Reduction in disease-causing protein



Natural

Harnesses natural cellular mechanisms present in every cell in the human body

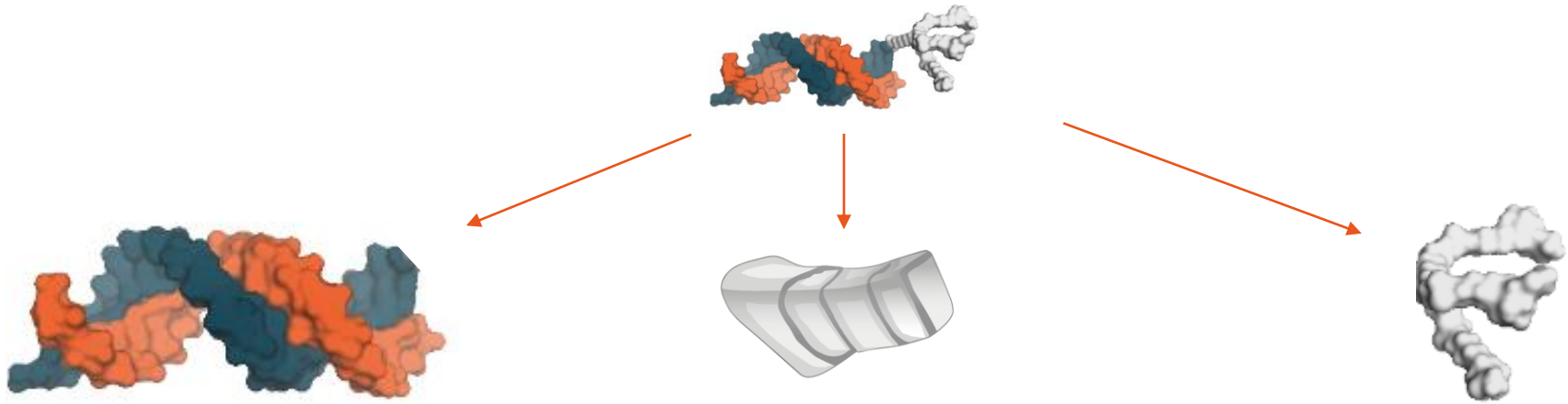
Durable

Long-lasting gene knockdown possible following a single injection

Precise

siRNA designed to bind only to target sequence

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

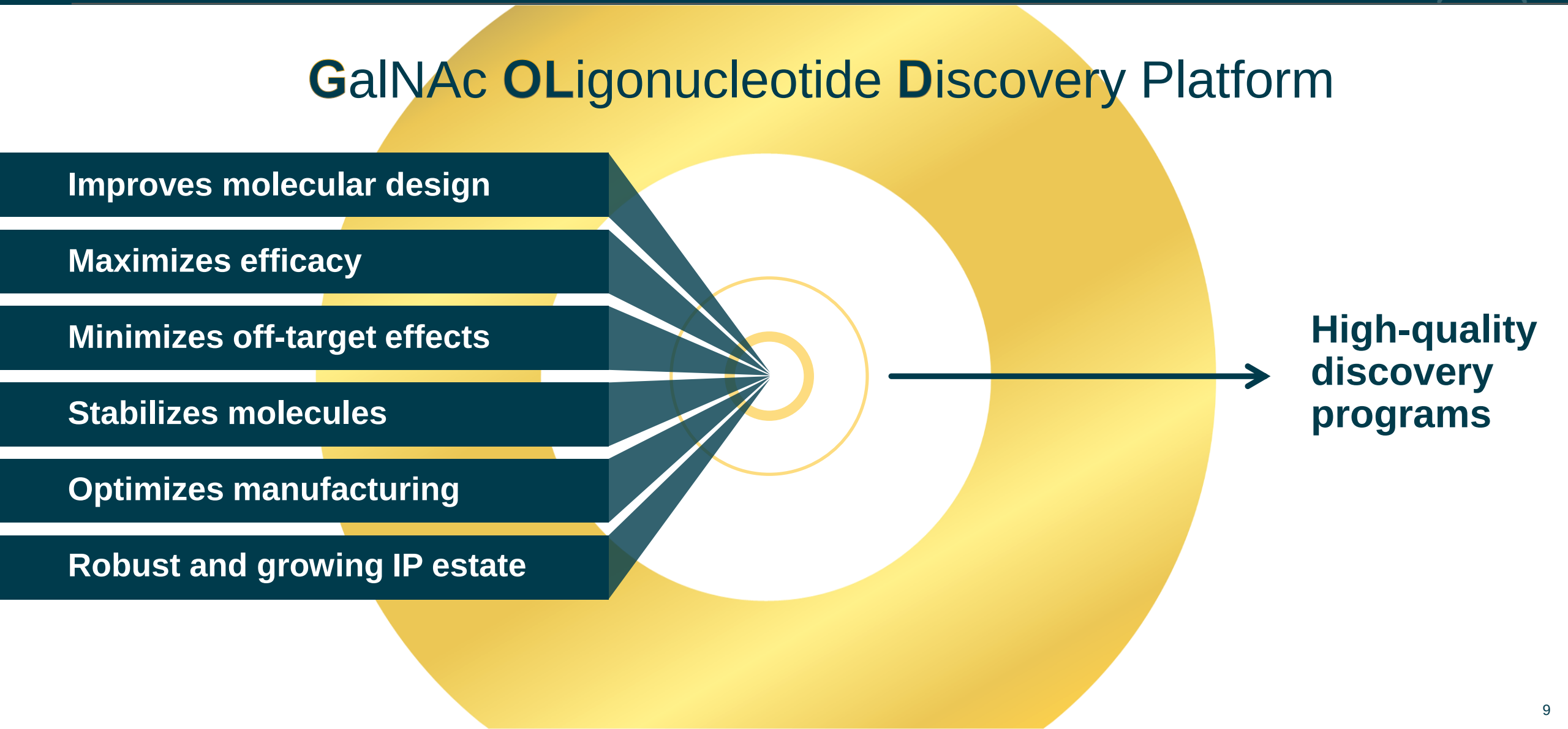
(delivery tool)

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

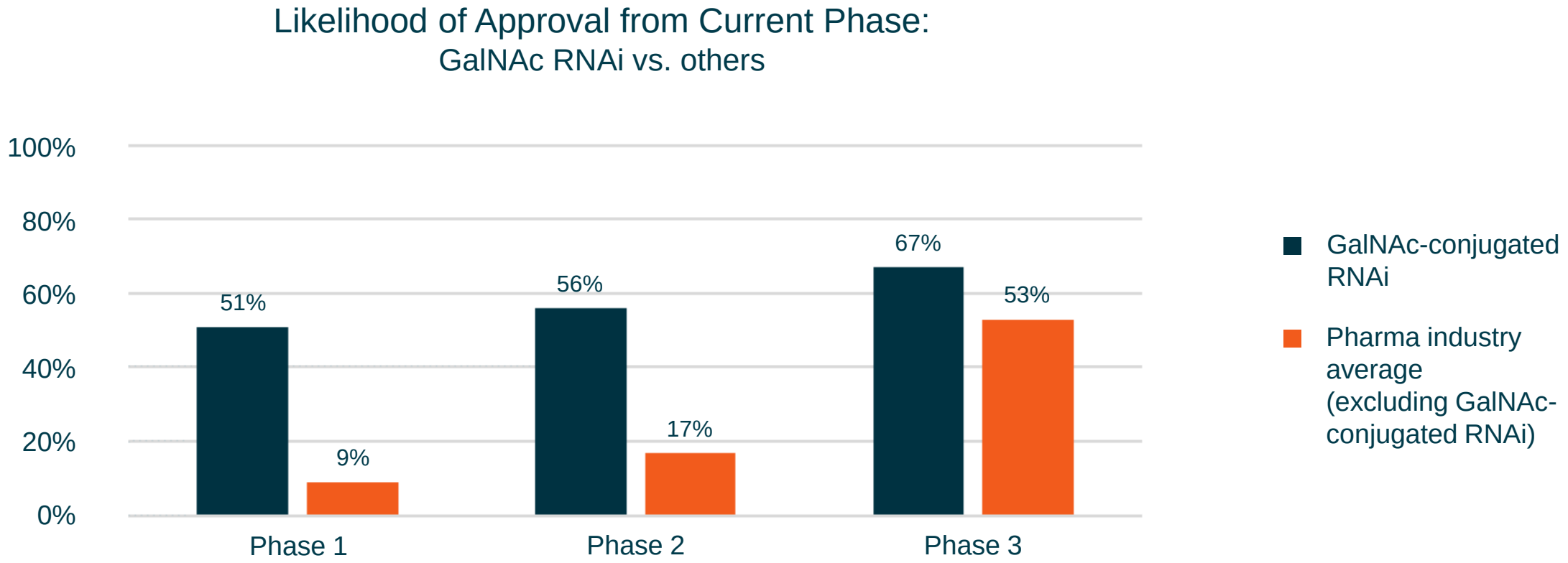
Continuous Fine-Tuning to Further Improve Performance

mRNAi GOLD™ Platform Approach: Precision-Engineered Therapies

GalNAc OLigonucleotide Discovery Platform



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 major 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

New collaboration to develop siRNA therapeutics for three undisclosed targets announced in Oct. 2021

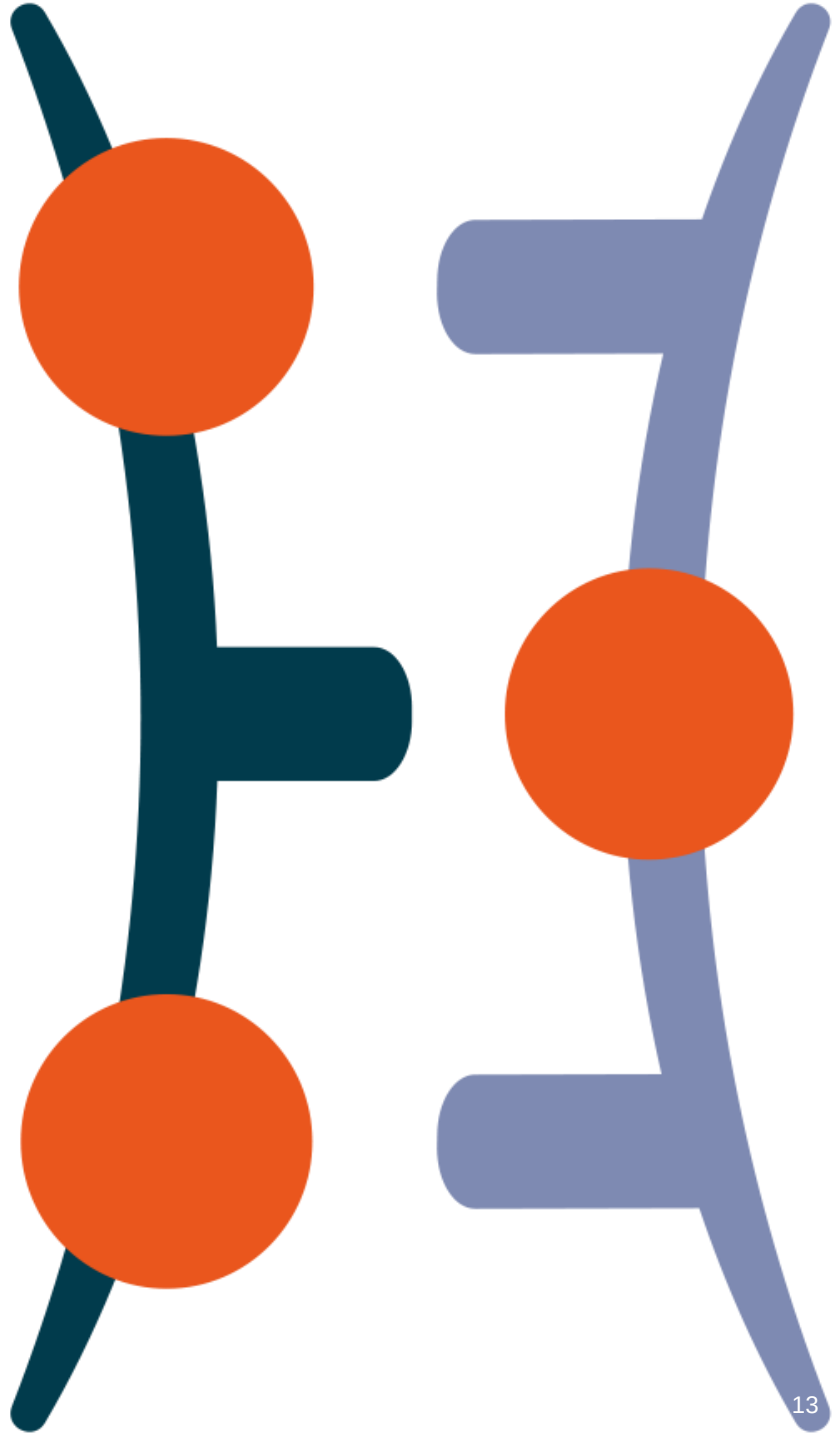
- Upfront cash payment of $16 million and up to $1.3 billion in potential milestones plus royalties
- Silence has exclusive rights to 2 targets in all territories except China region; Hansoh has China region rights to those 2 targets
- Hansoh has global rights to a third target

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



We've Now Generated Clinical Data in Two mRNAi GOLD™ Platform Programs

	Target	Ph 1 Study	Efficacy	Durability	Safety / Tolerability
SLN360	Lp(a)	32 healthy volunteers with high Lp(a)	Lp(a) reductions observed up to 98% after a single dose	Effects persisting at 150 days – longer term follow up ongoing	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 2 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

[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

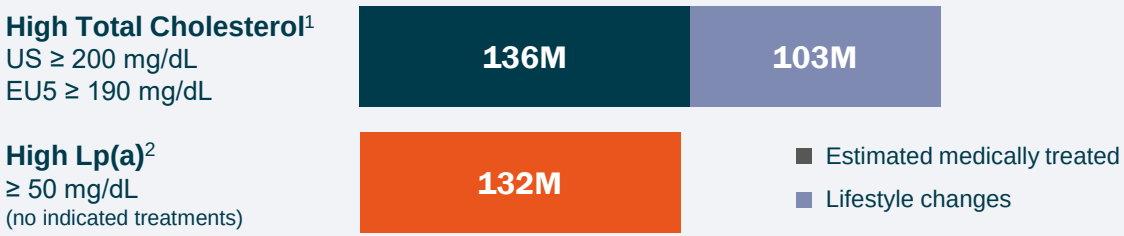
High Lp(a) is a Genetic Risk Factor

- Some patients require cholesterol lowering treatment: Lifestyle changes can have a positive impact
- Most patients will require Lp(a) lowering treatment: 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

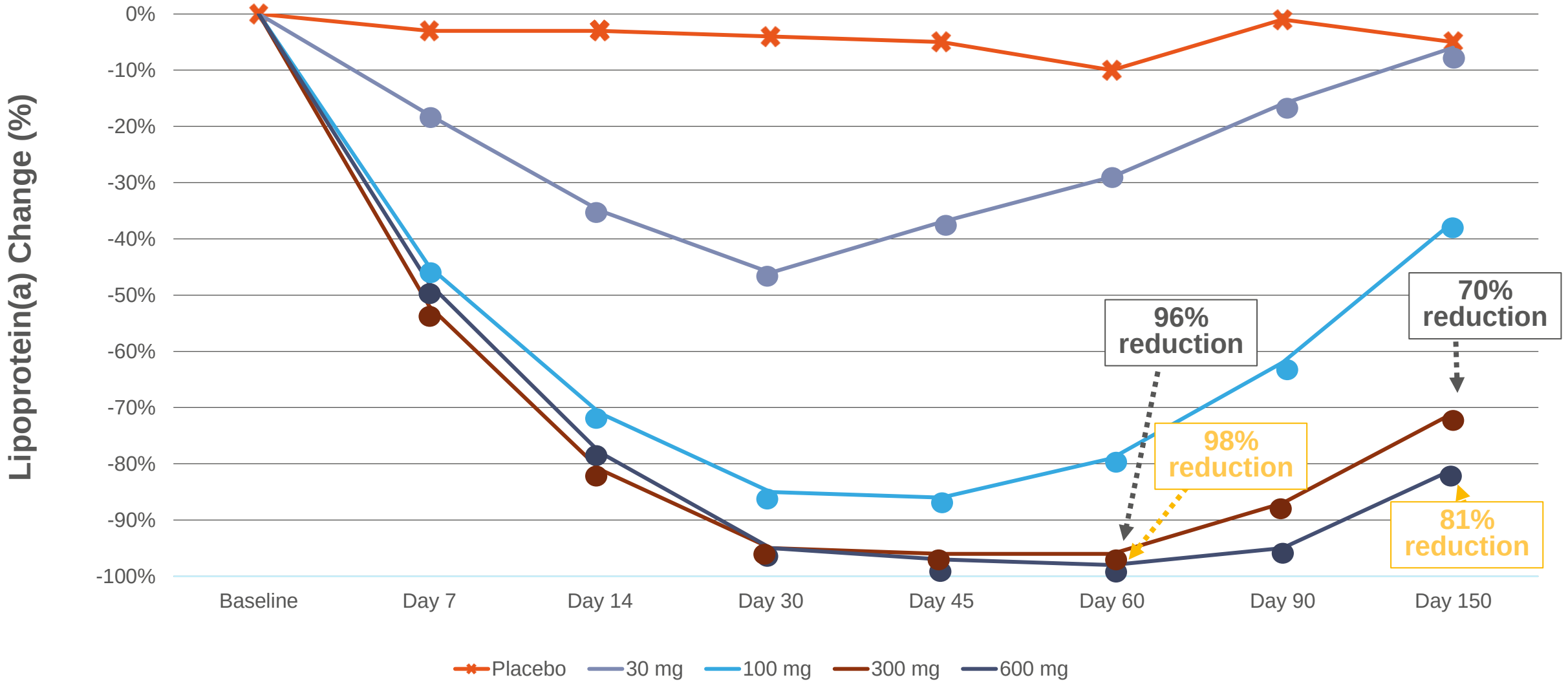
SLN360 Phase 1 Program Overview

Design	Global randomized, double-blind, placebo controlled single dose and multiple dose study
Aim	Investigate the safety, tolerability, PK and PD response of SLN360 in subjects with high Lp(a) ≥ 60 mg/dL
Single Dose Cohorts	32 healthy adults with high Lp(a) 8 subjects per cohort (6 active, 2 placebo)
Multiple Dose Cohorts	Adults with stable ASCVD and high Lp(a) 12 subjects per cohort (9 active, 3 placebo), up to 4 cohorts
Dosing	30 mg, 100 mg, ≥ 300 mg, ≥ 600 mg



PD = Pharmacodynamics; PK = Pharmacokinetics; ASCVD = atherosclerotic cardiovascular disease; MD = multiple dose; SD = single dose

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

SLN360 Demonstrated Excellent Results in Phase 1 Study in Healthy Adults with High Lp(a)

EFFICACY	SLN360 lowered Lp(a) up to 98% after a single dose
DURABILITY	>70% and >80% reductions in Lp(a) persisted for 150 days after the 300 mg and 600 mg doses
SAFETY	Well tolerated with no major safety issues



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

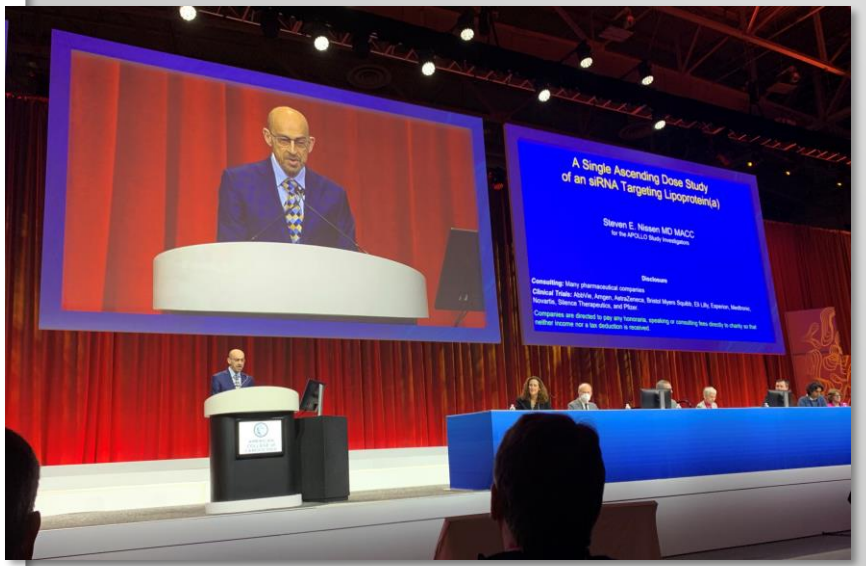
JAMA | Preliminary Communication

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

Next Steps for SLN360 Program

- Multiple dose arm of phase 1 APOLLO trial in patients with stable ASCVD underway
- Phase 2 ASCVD study expected to start by year end

ASCVD = atherosclerotic cardiovascular disease

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

Strong preclinical data showing therapeutic potential in several hematological disorders

Proof of mechanism demonstrated in healthy volunteer study

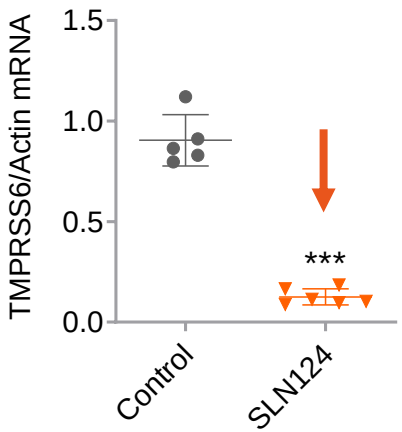
DESIGNATIONS

- ✓ Rare pediatric disease designation for beta thalassemia
- ✓ Orphan drug designations for beta thalassemia, polycythemia vera and MDS

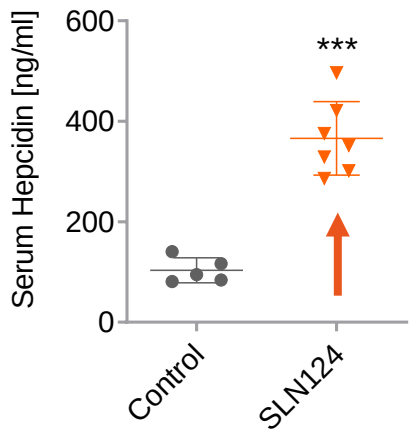
MDS = myelodysplastic syndrome

SLN124 is Designed to Restore Endogenous Hepcidin and Normalize Iron Levels

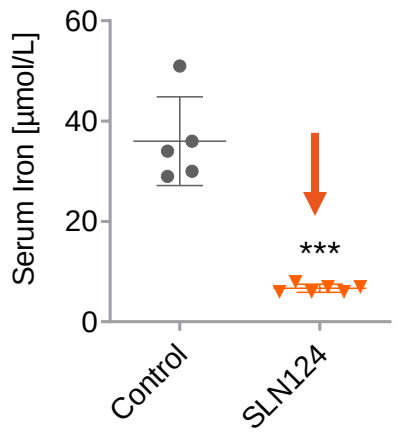
1 **Reduces TMPRSS6 in the liver**



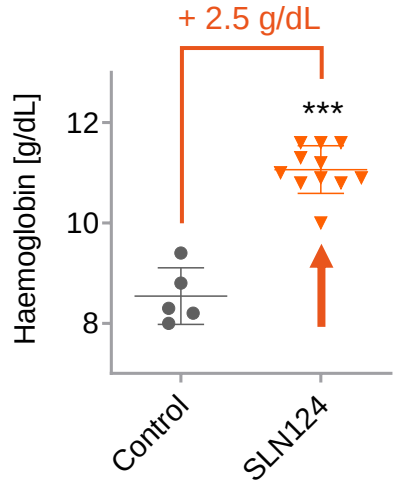
2 **Raises endogenous hepcidin**



3 **Lowers systemic iron levels and normalizes distribution**



4 **Improves red blood cell production**



SLN124 Aims to Reduce Anemia and the Need for Blood Transfusions and Iron Chelation Therapies

Study performed in a rodent model for beta thalassemia ($Hbb^{th3/+}$); *** p≤0.001

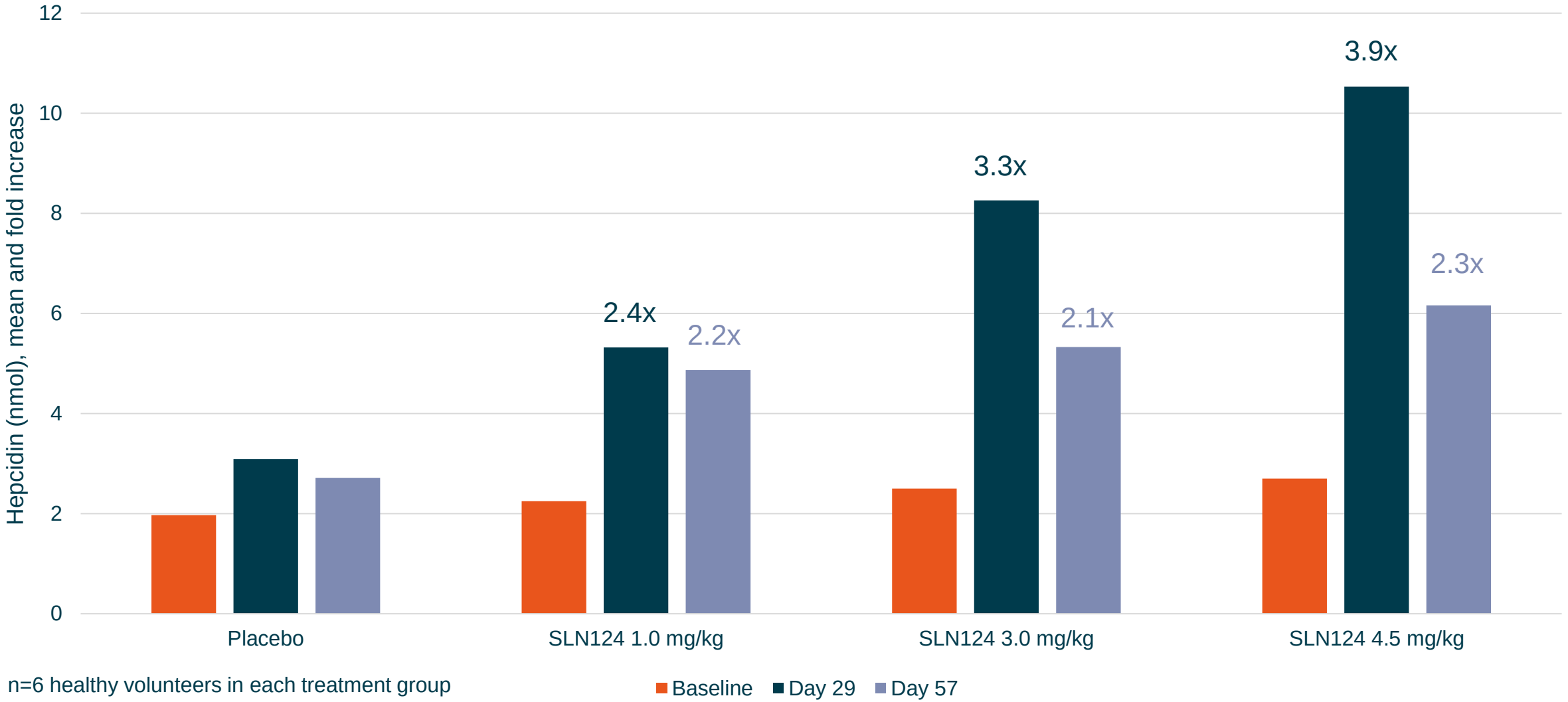
SLN124 Proof of Mechanism Established in Healthy Volunteer Study

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



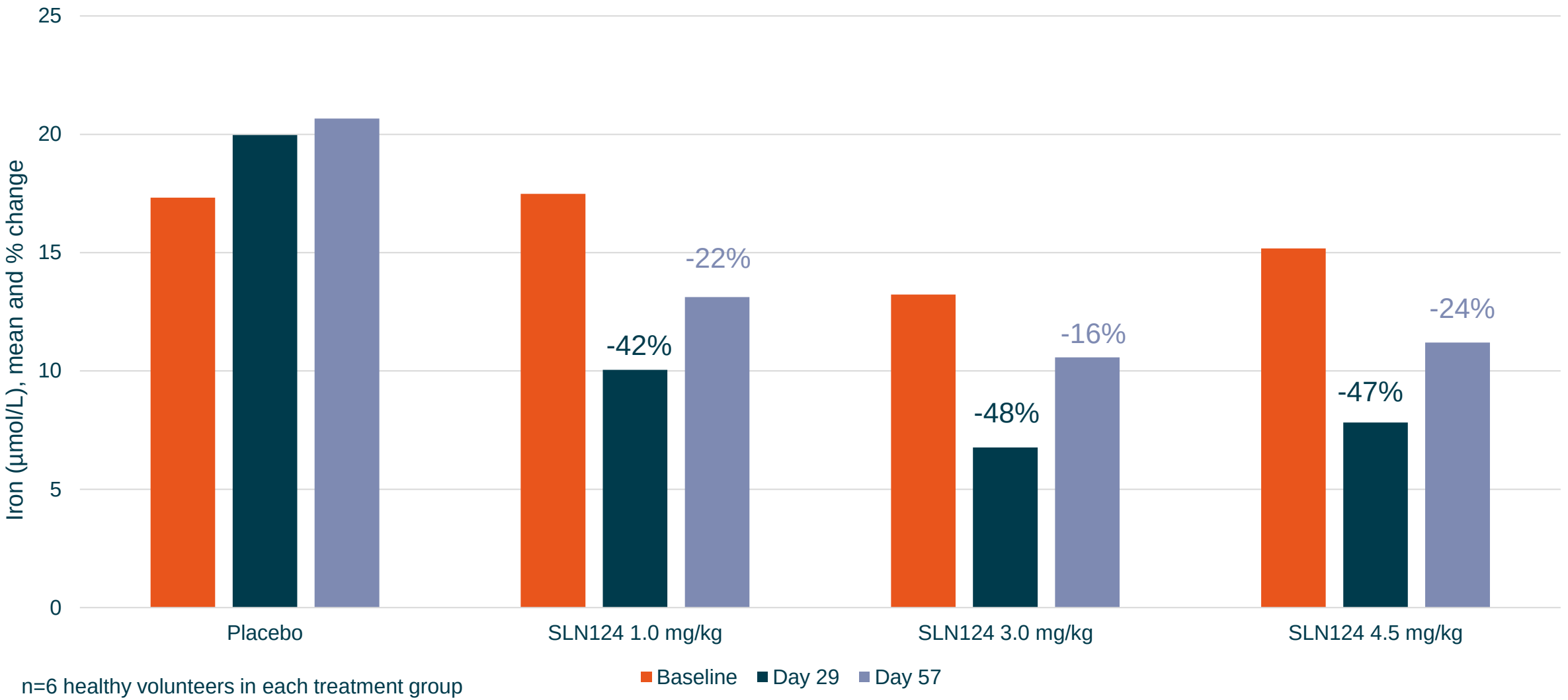
Data presented at ASH 2021

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



n=6 healthy volunteers in each treatment group

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



n=6 healthy volunteers in each treatment group

SLN124 Phase 1 Program in Adult Thalassemia

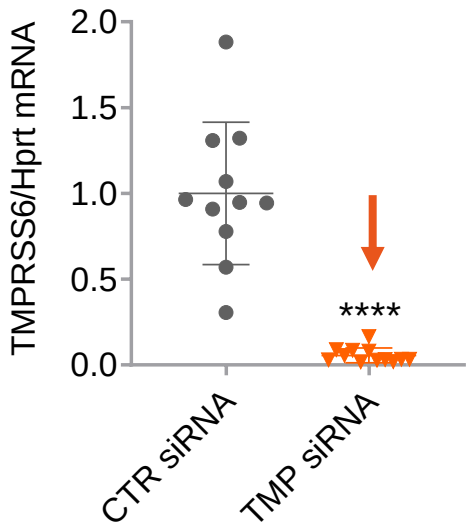
Design	Global, randomized, single-blind, placebo controlled single and multiple dose study
Aim	Investigate the safety, tolerability, PK and PD response of SLN124 in up to 56 adults with NTD thalassemia
Single Dose Cohorts	8 subjects per cohort, up to 4 cohorts
Multiple Dose Cohorts	8 subjects per cohort, up to 3 cohorts
Dosing	1 mg/kg, 3 mg/kg and ≤ 10 mg/kg



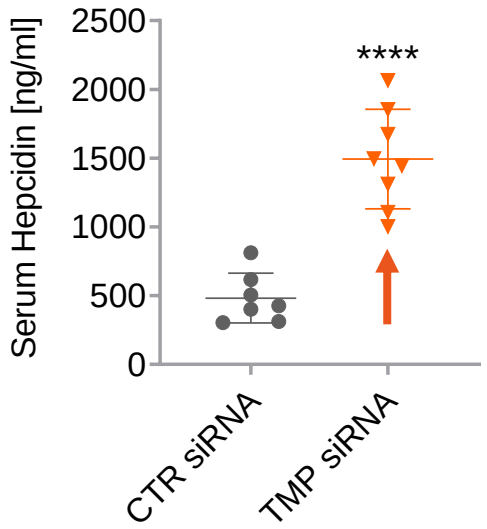
PD = Pharmacodynamics; PK = Pharmacokinetics; NTD = non-transfusion dependent

Promising Data of siRNA Driven TMPRSS6 Silencing in Mouse Model of Polycythemia Vera

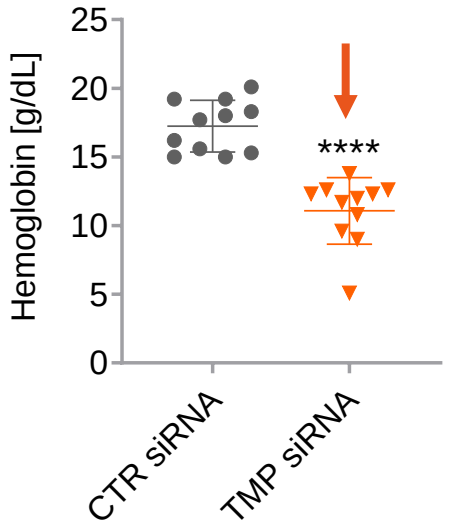
1 Reduces TMPRSS6 in the liver



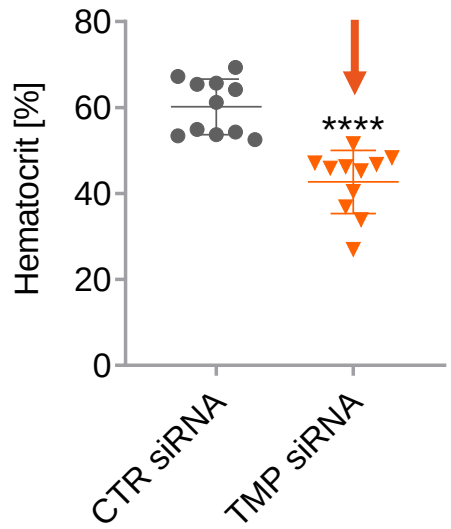
2 Raises endogenous hepcidin



3 Lowers hemoglobin



4 Reduces hematocrit



Study performed in a mouse model for polycythemia vera; **** p≤0.0001; CTR: control; presented at EHA 2021

Sant-Rayn Pasricha
Cavan Bennett

WEHI brighter together

Advancing Clinical Programs

Positive data in SLN360 study - late-breaker at ACC and JAMA publication

- Phase 2 ASCVD study expected to initiate by year-end, pending regulatory feedback

Engaged in global partnership discussions to maximize SLN360 program

- SLN124 thalassemia study fully enrolled; on-track for topline data in Q3 2022
- SLN124 granted FDA orphan drug designation for PV; phase 1 study to start in H2 2022

SLN501 (complement program with Mallinckrodt) phase 1 study initiated in H1 2022

ASCVD = atherosclerotic cardiovascular disease; PV = polycythemia vera

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 (7/8/22)	$11.20 per ADS
Common Shares Outstanding (3/31/22)	89,784,720 / ~29,928,240 ADS
Market Capitalization (7/8/22)	~$335m
Cash (3/31/22)	~$74m / £59m*
Debt	$0

*Does not include $5 million in collaboration milestones to be received in Q2’22
Notes: ADS each represent 3 ordinary shares nominal value