SILENCE THERAPEUTICS

Silence Therapeutics

Corporate Presentation

September 2021

Forward-Looking Statements

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Poised for Transformation

Major Clinical Data Readouts in Wholly Owned Programs Combined with Rapid Discovery Pipeline Growth

Pioneers in RNAi	• **Two decades of know-how combined with robust and growing IP estate** • **Global footprint – R&D in Berlin, headquarters in London and NYC office**

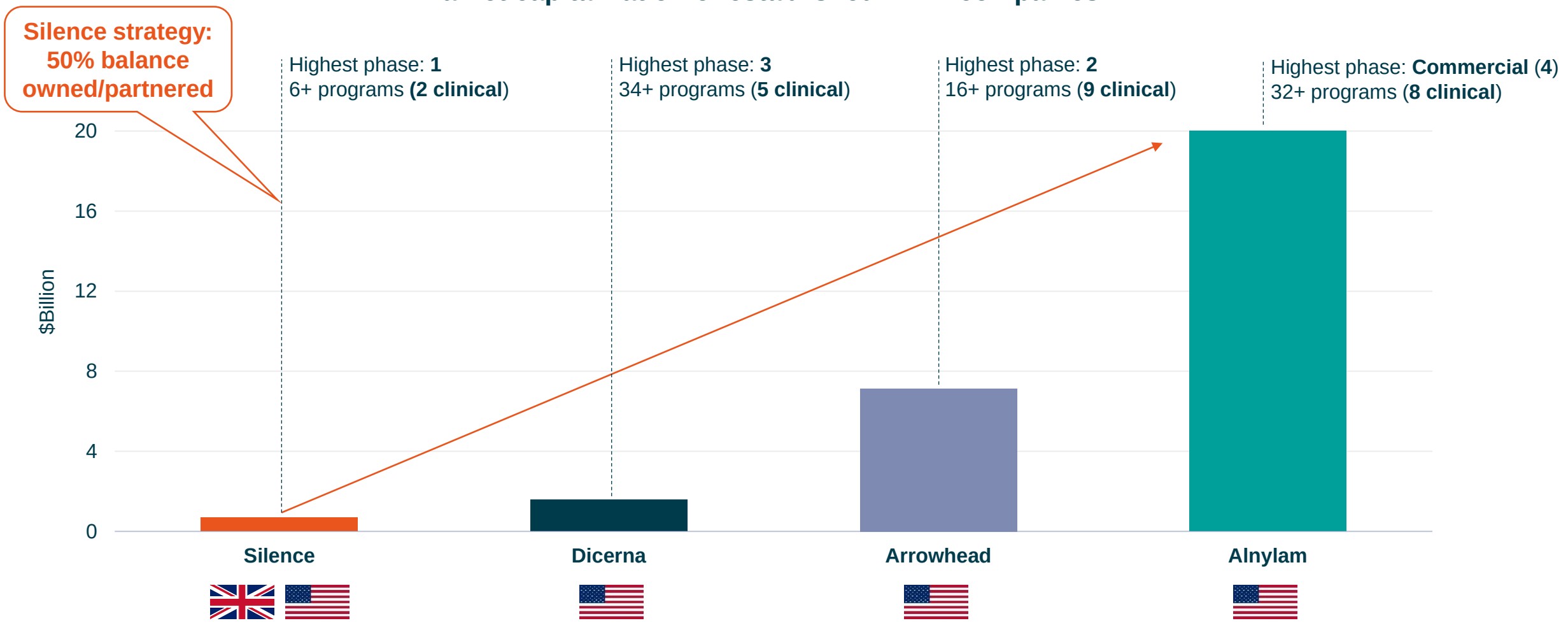
Rapidly Advance Clinical Programs	• **Positive topline healthy volunteer data in SLN124 program for iron-loading anemia conditions**
	• **Advancing two proprietary phase 1 clinical programs**
	  • SLN360 targeting high and prevalent unmet need in cardiovascular disease due to high lipoprotein(a)
	  • SLN124 targeting high unmet need in thalassemia and myelodysplastic syndrome

Proprietary mRNAi GOLD™ Platform	• **Clinical data demonstrated safety, robust pharmacodynamic effect and long duration of action** • **Anticipate 2-3 INDs per year from 2023 (proprietary and partnered programs)** • **Significant opportunity to address disease causing targets in the liver**
Strong Financial Position	• **£81.2m at the end of June 2021** • **AIM and Nasdaq listed (SLN) - market cap ~£500m /~$690m***

* Market Capitalization as of September 2, 2021

We believe the Path to Value Creation is Clear

Market capitalization of established RNAi companies



Market Capitalization as of September 2, 2021;
Programs include discovery phase through to marketed drugs, disclosed on company website and presentations 2Q 2021.

Executive Leadership Team with Deep Sector Experience



Mark Rothera

President and CEO

- 30+ years of experience in the biopharmaceutical industry
- Former President & CEO of Orchard Therapeutics and CCO of PTC Therapeutics
- Drove the transition of multiple emerging biotech companies from R&D stage to commercialization



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



Craig Tooman

Chief Financial Officer

- 30+ years of experience in the biopharmaceutical industry
- Over a decade of experience as public company CFO
- Proven track record raising capital and leading M&A deals



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. 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)

siRNA Can Inhibit Expression of Disease-Associated Genes

nucleus

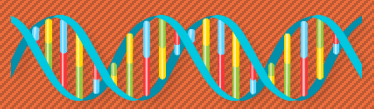
cytoplasm

HEALTHY

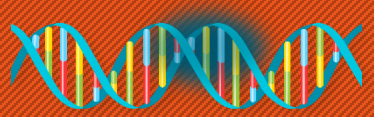
Genes encode messages for all features in the body

DISEASE

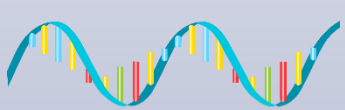
In certain diseases the DNA is mutated or abnormally expressed



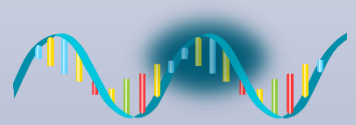
DNA



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

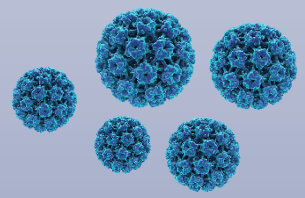


mRNA

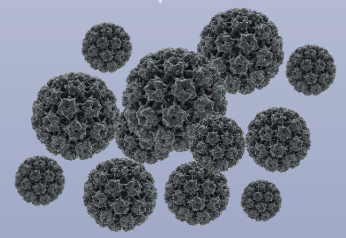


Abnormal DNA message is carried into resulting mRNA

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

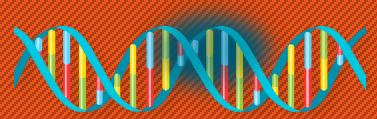


protein



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



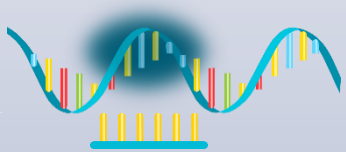
Mutated DNA

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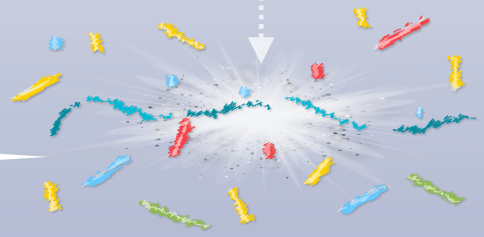
Target-specific short interfering RNA (siRNA) binds to the mRNA

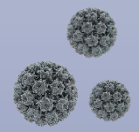
mRNA is degraded and gene is “silenced”

Reduction in disease-causing protein



mRNA





Natural

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

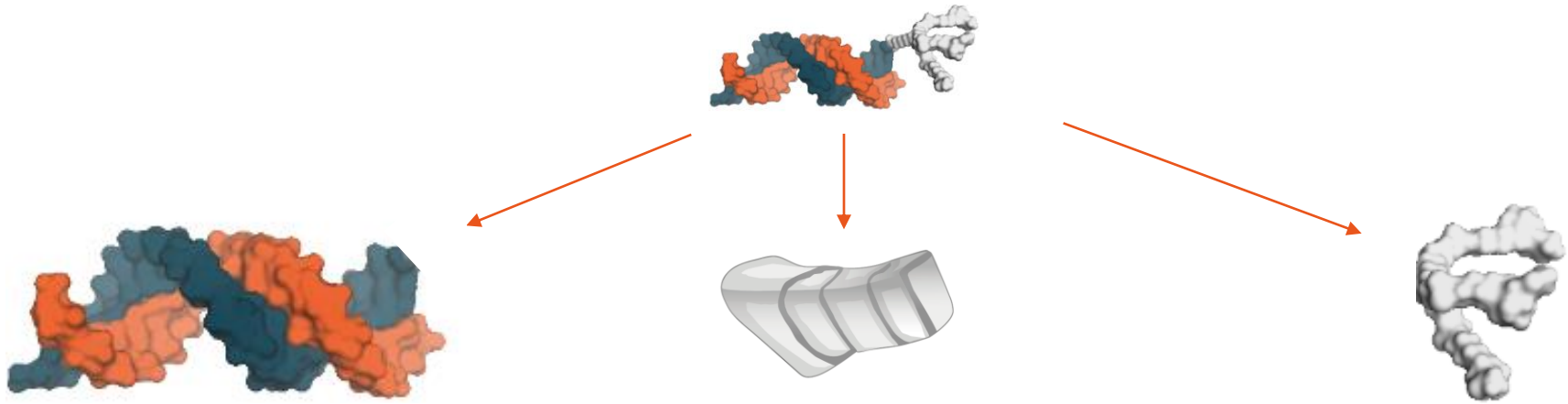
Durable

Long-lasting gene knockdown possible for > 2 months 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 modifications 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

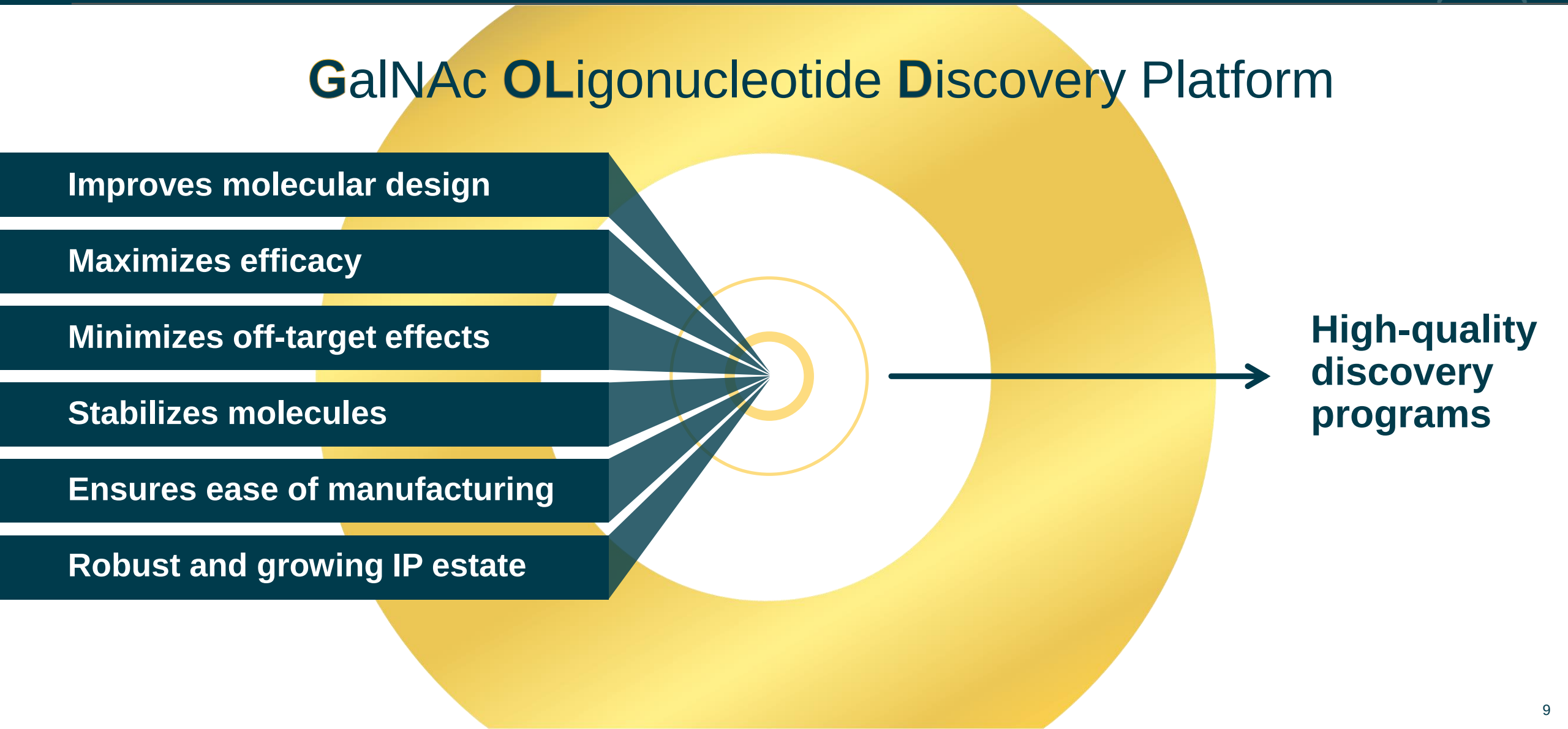
(delivery tool)

- 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

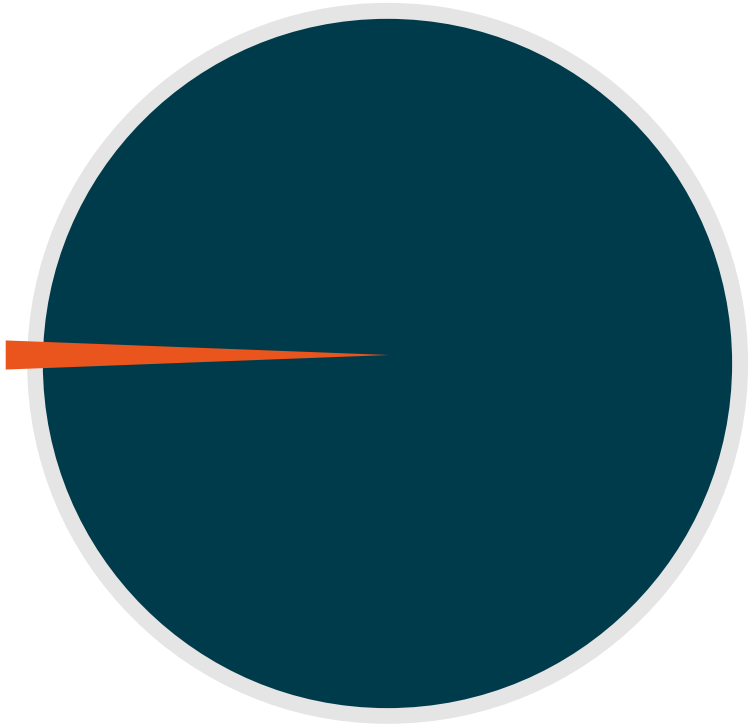
GalNAc OLigonucleotide Discovery Platform



We Believe the Opportunity for our mRNAi GOLD™ Platform is Substantial

Existing RNAi programs have only scratched the surface of the liver target space

Only ~1% of genes expressed in the liver have been targeted by publicly known siRNAs



Opportunity to identify new siRNAs targeting many of the remaining 99% (~14,000) of liver-expressed genes

Source: Human Protein Atlas, GlobalData

Our mRNAi GOLD™ Pipeline Targets

	Indication	Target	Discovery	Preclinical	Phase I	Phase II	Phase III	Proprietary/Partnered
SLN360	Cardiovascular disease with high Lp(a)	Lp(a)						SILENCE THERAPEUTICS
SLN124	Thalassemia	TMPRSS6						SILENCE THERAPEUTICS
SLN124	Myelodysplastic Syndrome	TMPRSS6						SILENCE THERAPEUTICS
Multiple programs	Undisclosed	Undisclosed						SILENCE THERAPEUTICS
SLN501	Complement-mediated diseases	C3						Mallinckrodt
SLN-MNK-2	Complement-mediated diseases	2nd complement target						
SLN-MNK-3	Complement-mediated diseases	3rd complement target						
SLN-AZ-1	Undisclosed	Undisclosed						AstraZeneca
SLN-AZ-2	Undisclosed	Undisclosed						

Maximizing Output through the Silence mRNAi GOLD™ Platform

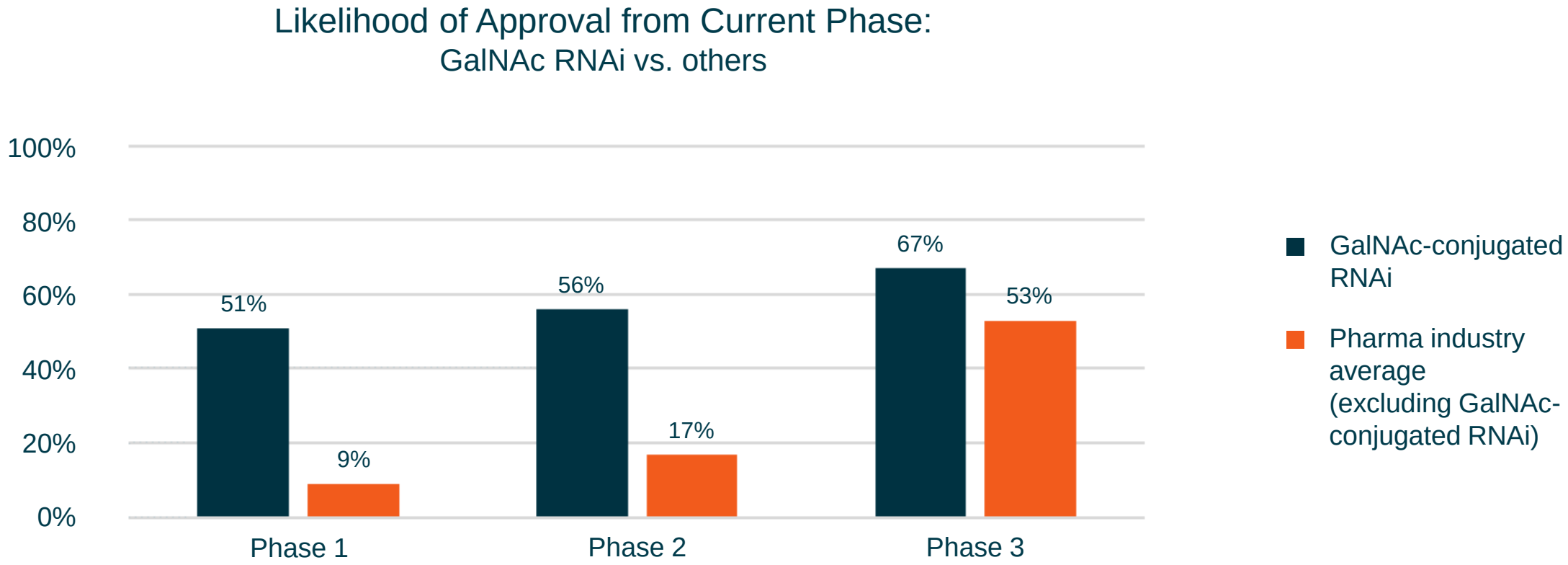
- **High-quality target identification** using translational genomics
- **Lower attrition rates** in discovery enabled by machine learning
- **GalNAc strategic partnerships** to enhance pipeline opportunities (e.g. target selection)

Targeting

2-3 INDs/yr

from 2023 through our proprietary and partnered GalNAc 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

Upcoming Events & Anticipated Milestones

	H1 2021	H2 2021	H1 2022	H2 2022
SLN360 for CVD due to high Lp(a) levels	✓ Started dosing in single-ascending dose study	✓ Fully enrolled 4 cohorts of single-ascending dose study	★ Topline data in single-ascending dose study (4 cohorts)	
SLN124 for thalassemia and MDS	✓ Started dosing in single-ascending dose studies ✓ Reported positive topline data in healthy volunteer study	★ Present more data from healthy volunteer study		★ Topline data in single-ascending dose studies

R&D Day in NYC on October 21st

✓ = milestone achieved

★ = data milestone

Note: all programs are at potential risk of delay due to COVID-19

CVD: cardiovascular disease; MDS: myelodysplastic syndrome

SLN360

for Cardiovascular Disease
Due to High Lp(a)



SLN360 Targets Lipoprotein(a) or 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 through lifestyle changes or approved medicines

Large population worldwide with up to 10% with >90mg/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

Lp(a)-lowering Drugs Present a Similar Opportunity to Cholesterol-lowering Drugs, Which Had Sales of >$30B at Peak

High Cholesterol vs High Lp(a) in Cardiovascular Disease

High Cholesterol is a Modifiable Risk Factor

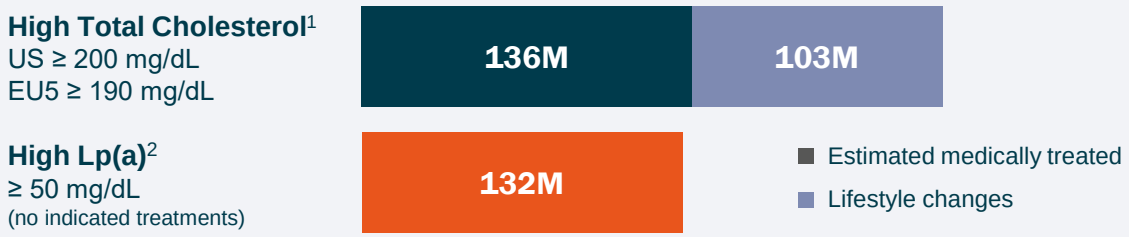
High Lp(a) is a Genetic Risk Factor

- 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

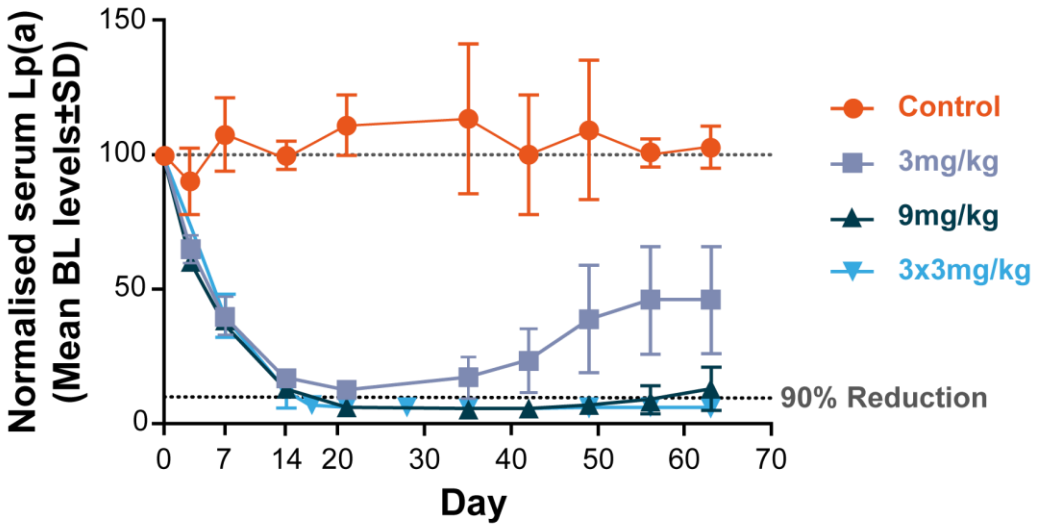
Sales of Cholesterol-Lowering Drugs Peaked at >$30B[3,4]

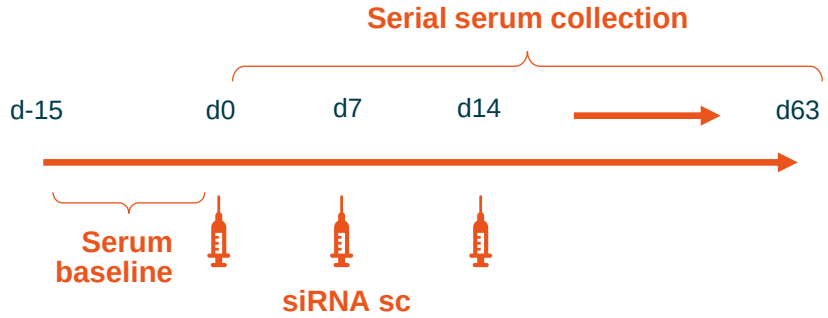
Lipitor® (atorvastatin)	**Crestor®** (rosuvastatin)	**Zocor®** (simvastatin)
$12.9B peak sales	**$7.0B** peak sales	**$5.2B** peak sales

[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 Demonstrated Sustained and Deep Lp(a) Knockdown in Non-Human Primate Model

Serum Lp(a) reduction





Group	mg/kg	Days
1	0	0
2	3	1
3	9	1
4	3	1, 7, 14

SLN360 demonstrated ideal profile in NHP model

Efficacy: Robust Lp(a) knockdown observed after first dose (>90%)

Durability: Sustained reduction of Lp(a) serum levels (>90%) for duration of study

Safety: <1% exposure outside liver with no detected off target effects

SLN360 Phase 1 Program Overview

Design	Global randomized, double-blind, placebo controlled single-ascending dose and multiple dose study
Aim	Investigate the safety, tolerability, PK and PD response of SLN360 in subjects with high Lp(a)
Single-Ascending Dose Cohorts	8 subjects per cohort (6 active, 2 placebo), up to 5 cohorts
Multiple-Ascending Dose Cohorts	12 subjects per cohort (9 active, 3 placebo), up to 4 cohorts
Dosing	30 mg, 100 mg, ≤ 300 mg, ≤ 600 mg and ≤ 900 mg
Population	88 subjects total with high Lp(a) approximately ≥ 60 mg/dL



PD: Pharmacodynamics; PK: Pharmacokinetics

SLN124

for Iron-Loading Anemia Conditions



SLN124: Addressing a Major Unmet Need in Thalassemia and Myelodysplastic Syndrome (MDS)

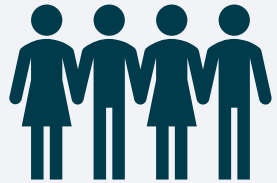
MYELODYSPLASTIC SYNDROME (MDS)

Prevalence[1]: ~160,000 pts
(US+EU5)

Onset: Later in life (60+)

☑ Orphan Drug Designation

- Group of rare malignant blood disorders that impact older patients
- Low quality of life and poor response to current therapies
- Burdens include severe anemia, transfusion dependence, toxic iron overload
- Progression to acute myeloid leukemia (30% of MDS patients)



THALASSEMIA

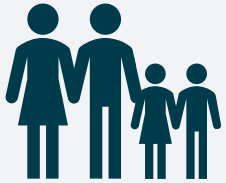
Prevalence[2]: ~35,000 pts
(US+EU5) TDT and NTDT

Onset: **TDT:** early childhood
NTDT: teens or later

☑ Orphan Drug Designation

☑ Rare Pediatric Disease Designation

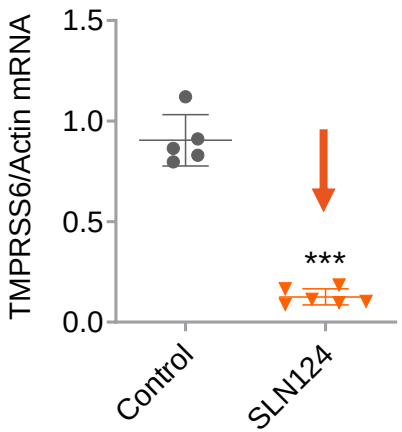
- A rare genetic blood disorder that affects children and adults
- The majority are dependent on regular blood transfusions (TDT), while others are transfused less frequently (NTDT)
- Severe limitations and low quality of life with current treatments
- Opportunity to improve quality of life by reducing the frequency of blood transfusions
- Burdens include severe anemia, transfusion dependence, toxic iron overload



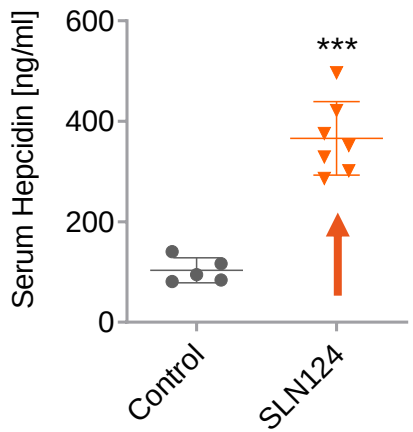
[1] Internal analysis; [2] Kattamis et.al, Eur J Haematol. 2020;105:692; TDT: transfusion-dependent thalassemia; NTDT: non- transfusion-dependent thalassemia

SLN124 is Designed to Restore Endogenous Hepcidin and Normalize Iron Levels

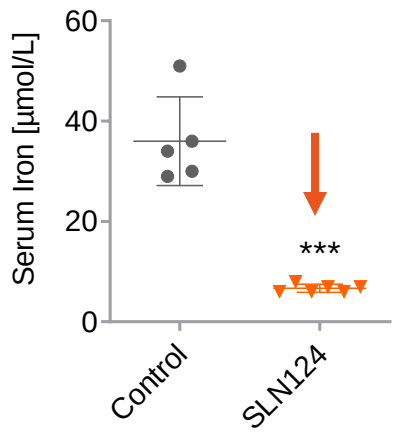
1 **Reduces TMPRSS6 in the liver**



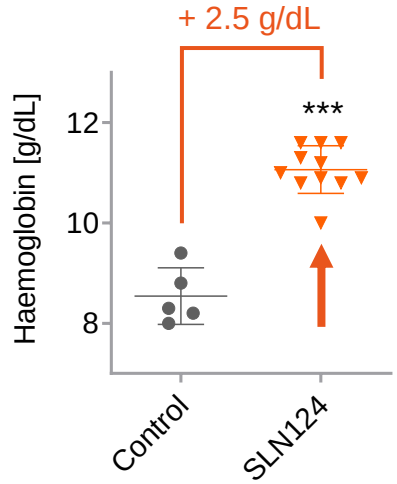
2 **Raises endogenous hepcidin**



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 Phase 1 Healthy Volunteer Study Design

Design	Randomized, double-blind, placebo controlled, single-ascending dose study
Aim	Investigated the safety, tolerability, PK and PD response of SLN124 in healthy volunteers
Single-Ascending Dose Cohort	3 cohorts, 8 subjects per cohort (6 active, 2 placebo)
Dosing	1 mg/kg, 3 mg/kg and 4.5 mg/kg
Population	24 healthy adults

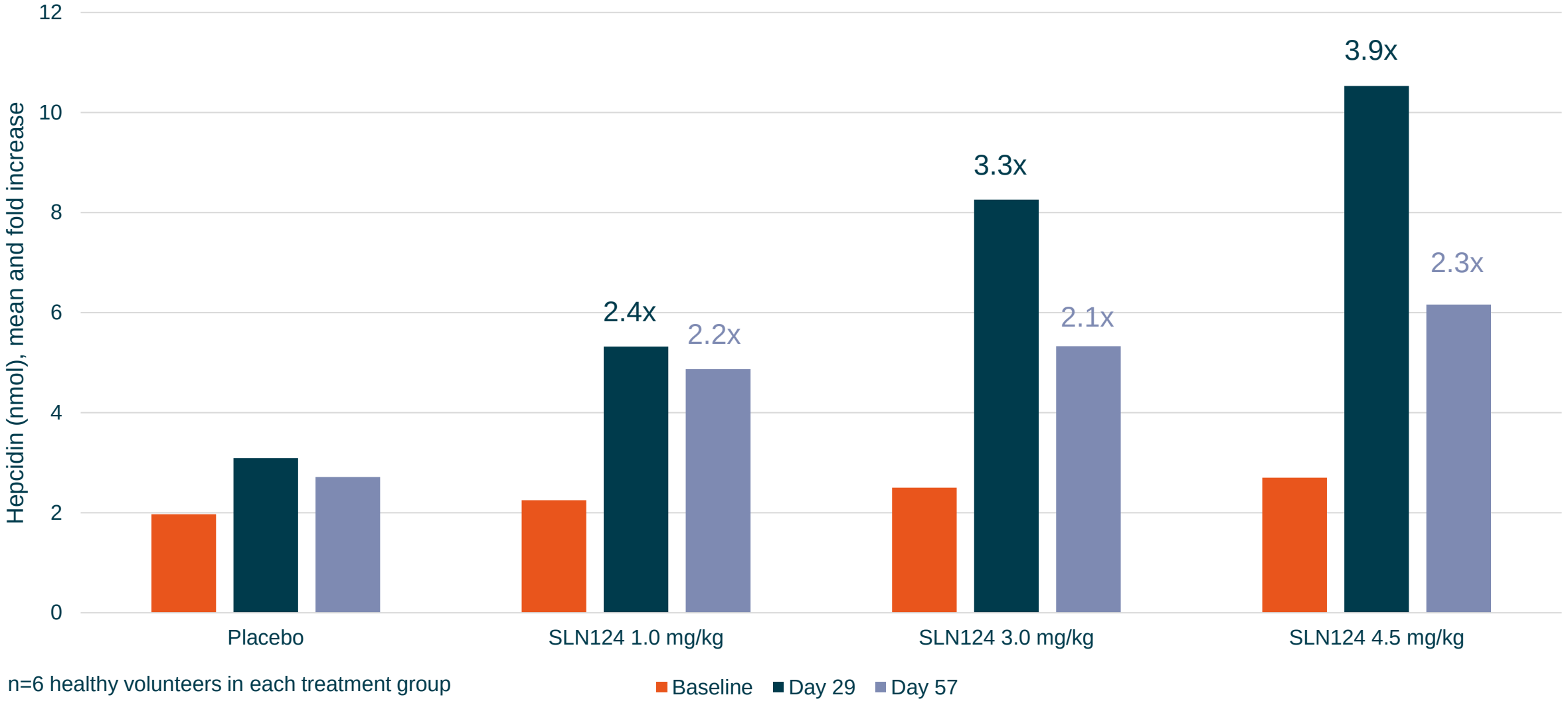


PD: Pharmacodynamics; PK: Pharmacokinetics

Positive Results from SLN124 Healthy Volunteer Study

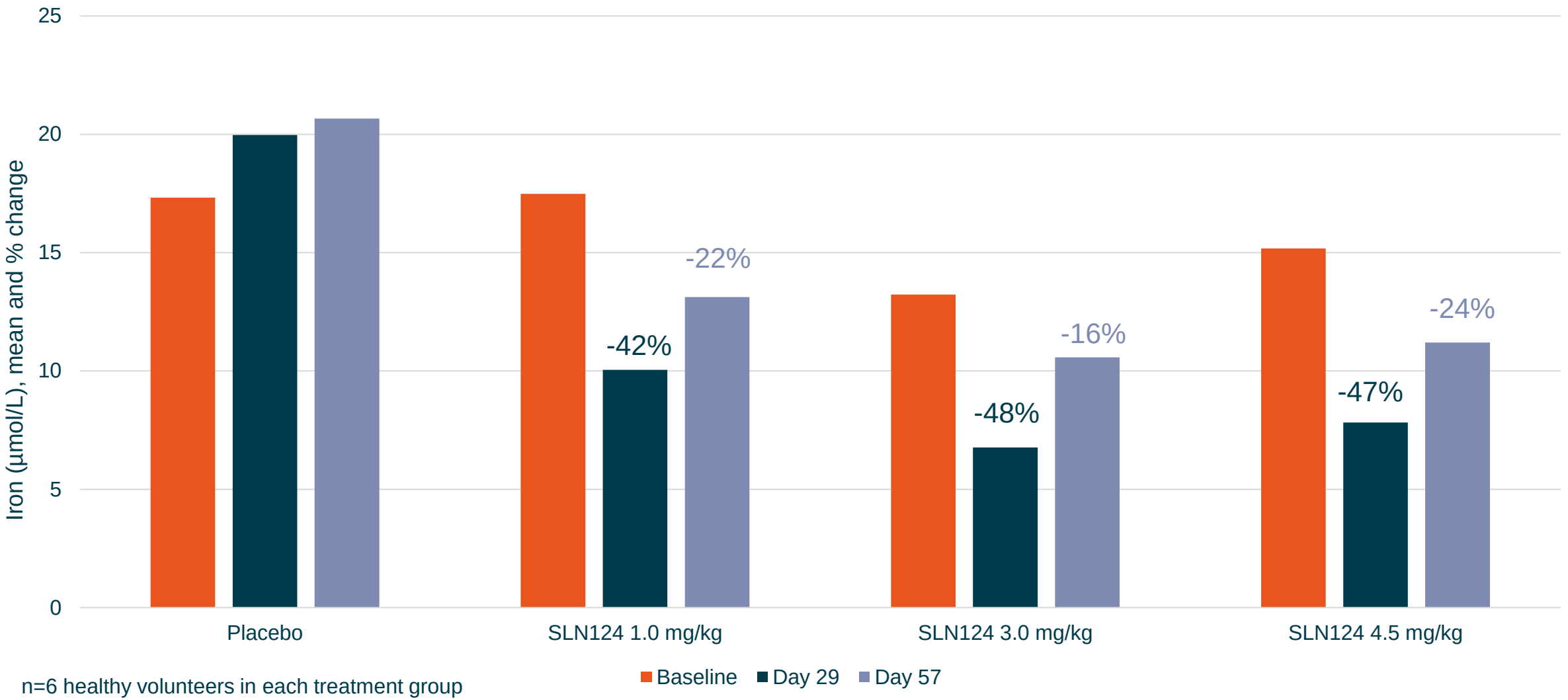
- First clinical data from **mRNAi GOLD™** platform
- Demonstrated proof of mechanism for SLN124
- All 3 dose levels of SLN124 were safe and generally well-tolerated
  - No serious or severe treatment emergent adverse events (TEAEs) or TEAEs leading to withdrawal
  - Majority of TEAEs were mild, including transient injection site reactions which resolved without intervention
- SLN124 increased average hepcidin up to ~4-fold after a single dose with effect sustained for at least 2 months
- SLN124 reduced serum iron by ~50% after a single dose with effect sustained for at least 2 months

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 and MDS

Design	Global, randomized, single-blind, placebo controlled single-ascending and multiple-ascending dose studies
Aim	Investigate the safety, tolerability, PK and PD response of SLN124 in adults with thalassemia and MDS
Single-Ascending Dose Cohorts	8 subjects per cohort (6 active, 2 placebo), up to 4 cohorts per study
Multiple-Ascending Dose Cohorts	8 subjects per cohort (6 active, 2 placebo), up to 3 cohorts per study
Dosing	1 mg/kg, 3 mg/kg and ≤ 10 mg/kg
Population	up to 112 adults with non-transfusion dependent thalassemia and VL/LR-MDS

GEMINI II

MDS: myelodysplastic syndrome; PD: Pharmacodynamics; PK: Pharmacokinetics; VL/LR-MDS: very low- and low-risk MDS

Partnership Programs Further Expand Pipeline and Provide Up to $6 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[1]
- 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

Expanded complement pathway RNAi collaboration in July 2020

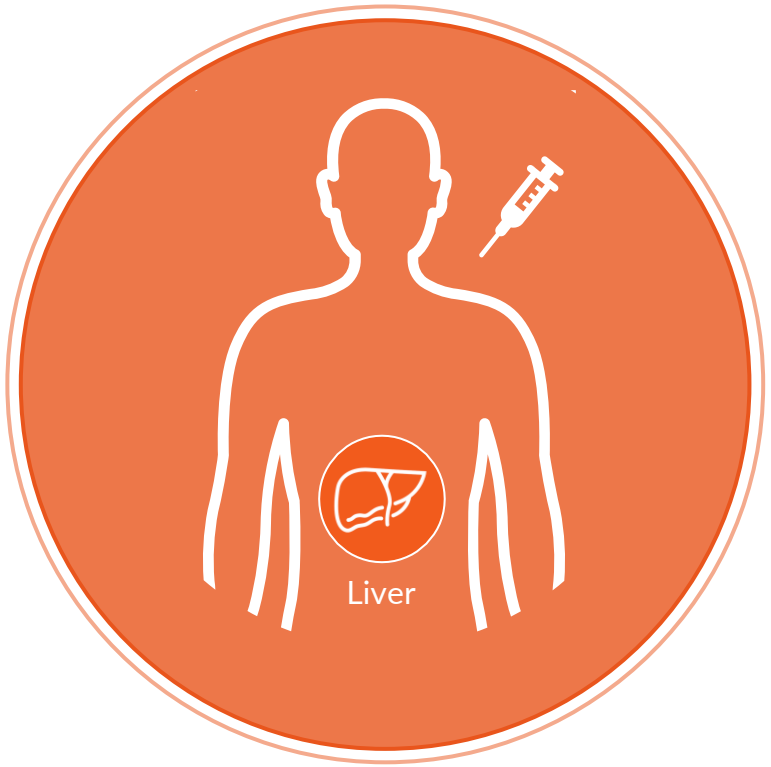
- Upfront cash payment of $20 million and an equity investment of $5 million
- Up to $2 billion in potential milestones plus royalties for 3 targets
- Exercised option to license 3 complement targets ($2M per target)

Commenced technology evaluation to explore the potential of using our platform to generate siRNA molecules against a novel, undisclosed target in January 2020

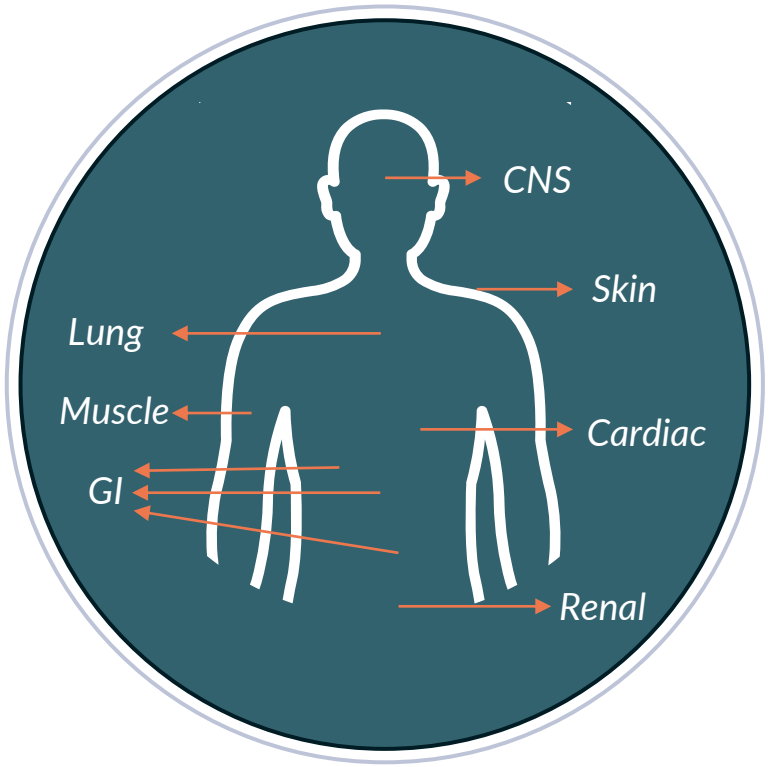
[1] Of the $60m, $20m was paid in May 2020 and a further $40m was paid in H1 2021.

Developing a New Extra-Hepatic siRNA Delivery Platform

PRESENT



FUTURE



Tap into the huge opportunity to silence genes outside of the liver

Financial Highlights

(SLN:AIM) and (SLN:Nasdaq)	
Stock Price (09/02/21)	545p / $22.60
Common Shares Outstanding (6/30/21)	89,735,448
Market Capitalization (09/02/21)	~£500m /~$690m
Cash (6/30/21)	£81.2m
Debt	$0