SILENCE THERAPEUTICS

Silence Therapeutics

Corporate Presentation

January 2022

Forward-Looking Statements

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Poised for Transformation

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

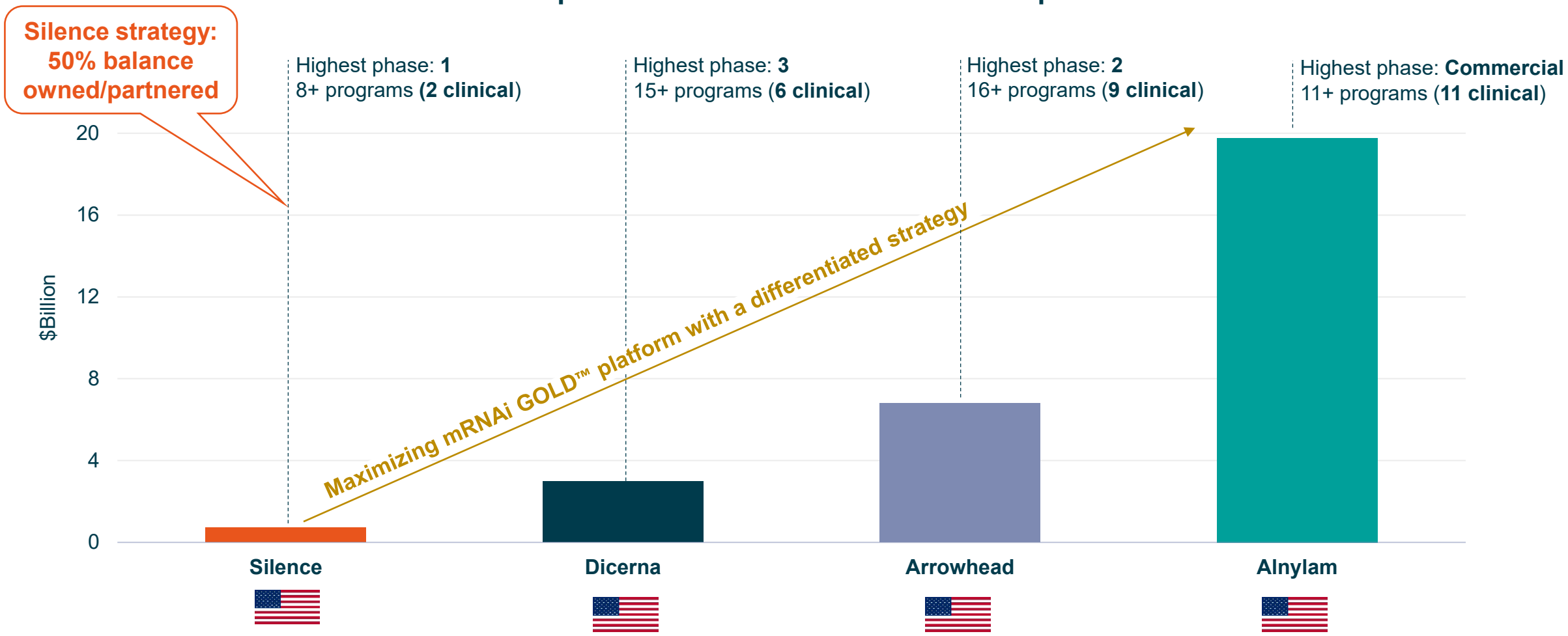
Pioneers in RNAi	• **Two decades of know-how combined with robust and growing IP estate** • **Global footprint – R&D in Berlin, headquarters in London and NYC office**
Rapidly Advance Clinical Programs	• **SLN360 Lp(a) Lowering Program** - topline data anticipated this quarter; initiating phase 2 in H2'22 • **SLN124 Hepcidin Regulation Program** – topline data from thalassemia and MDS studies anticipated in Q3'22; initiating phase 1 PV study in H2'22 • **SLN501 C3 Lowering Program** – initiating phase 1 study with Mallinckrodt in H1'22
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	• **£76.5m at the end of September 2021** • **Nasdaq listed (SLN) - market cap ~£525m /~$712m***

* Market Capitalization as of January 4, 2022

Lp(a) = Lipoprotein(a); MDS = myelodysplastic syndrome; PV = polycythemia vera

We believe the Path to Value Creation is Clear

Market capitalization of established RNAi companies



Market Capitalization as of January 4, 2022;
Programs defined as individually named programs from discovery phase through to marketed drugs on company website, October 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

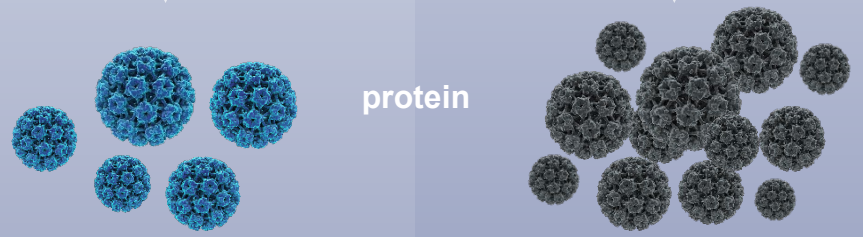


The information in DNA is transcribed into messenger RNA (mRNA)



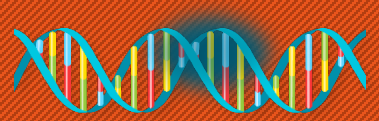
Abnormal DNA message is carried into resulting mRNA

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



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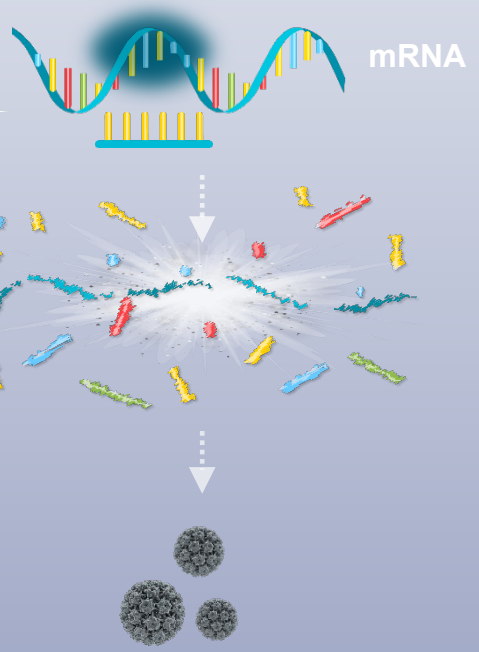
Target-specific short interfering RNA (siRNA) binds to the mRNA

mRNA is degraded and gene is “silenced”

Reduction in disease-causing protein



Natural

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

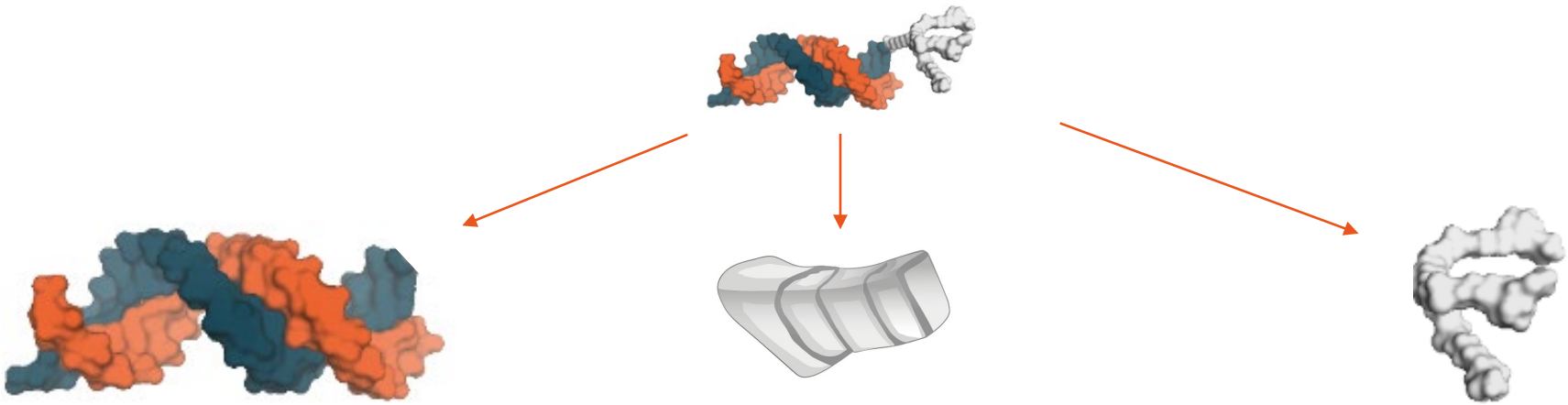
Durable

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 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

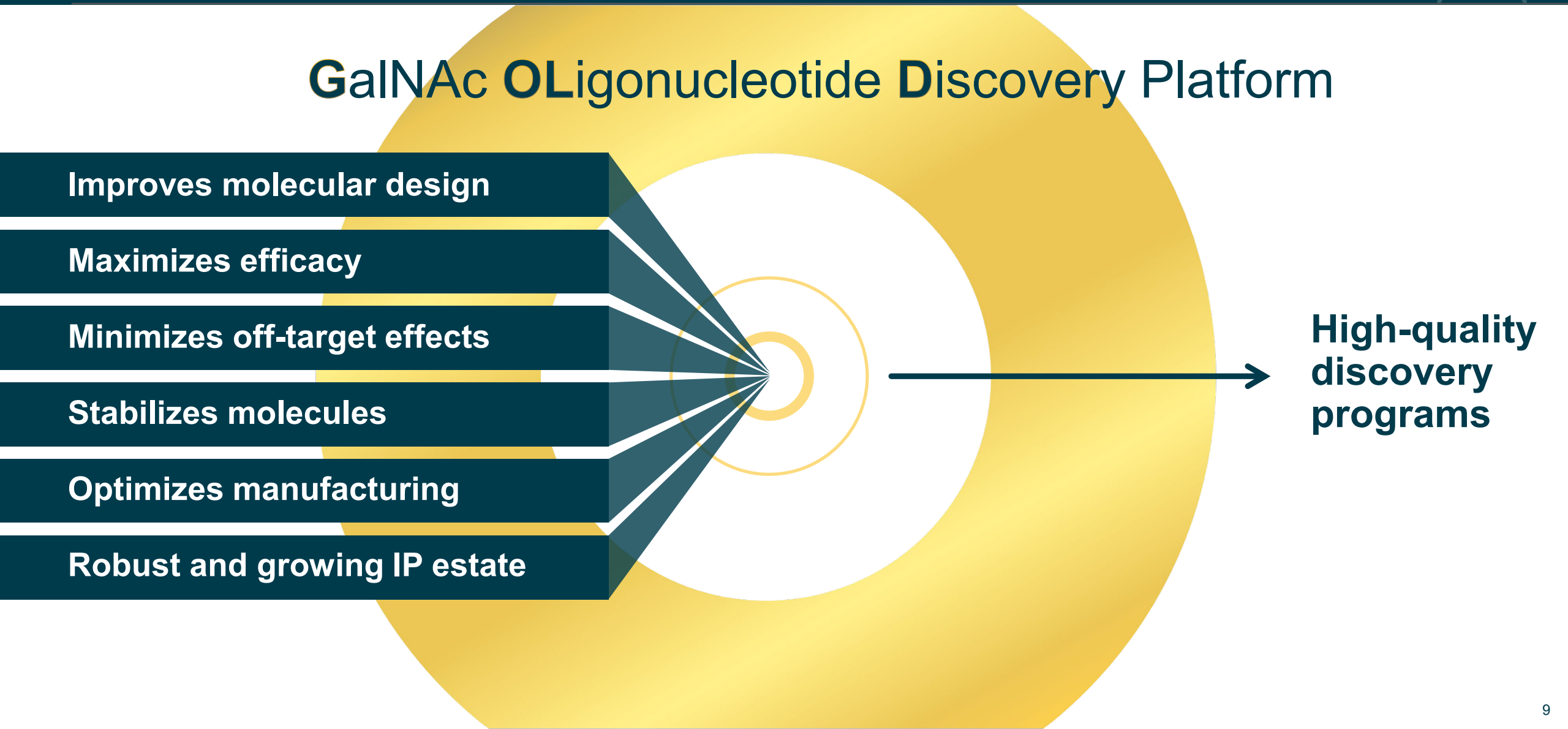
(delivery tool)

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

Continuous Fine-Tuning to Further Improve Performance

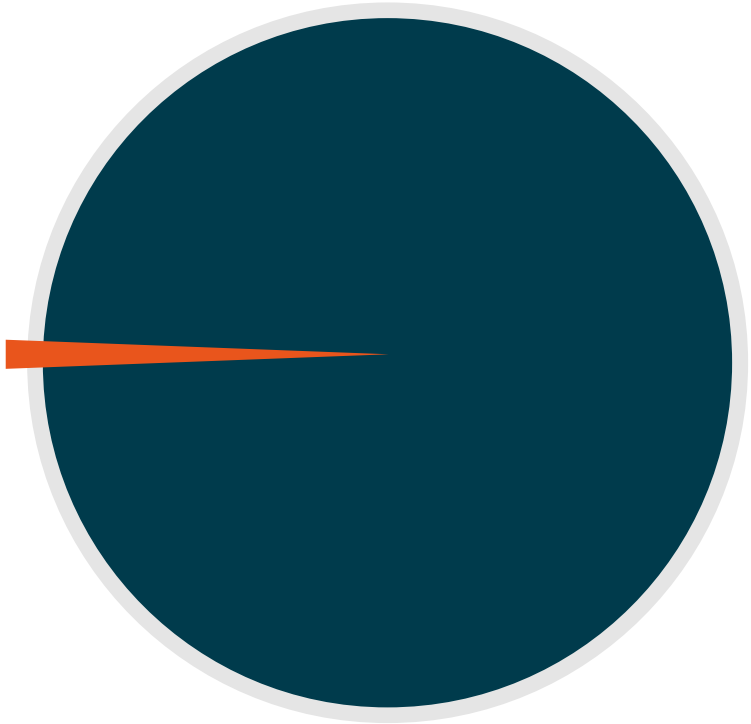
mRNAi GOLD™ Platform Approach: Precision-Engineered Therapies

GalNAc OLigonucleotide Discovery Platform



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

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

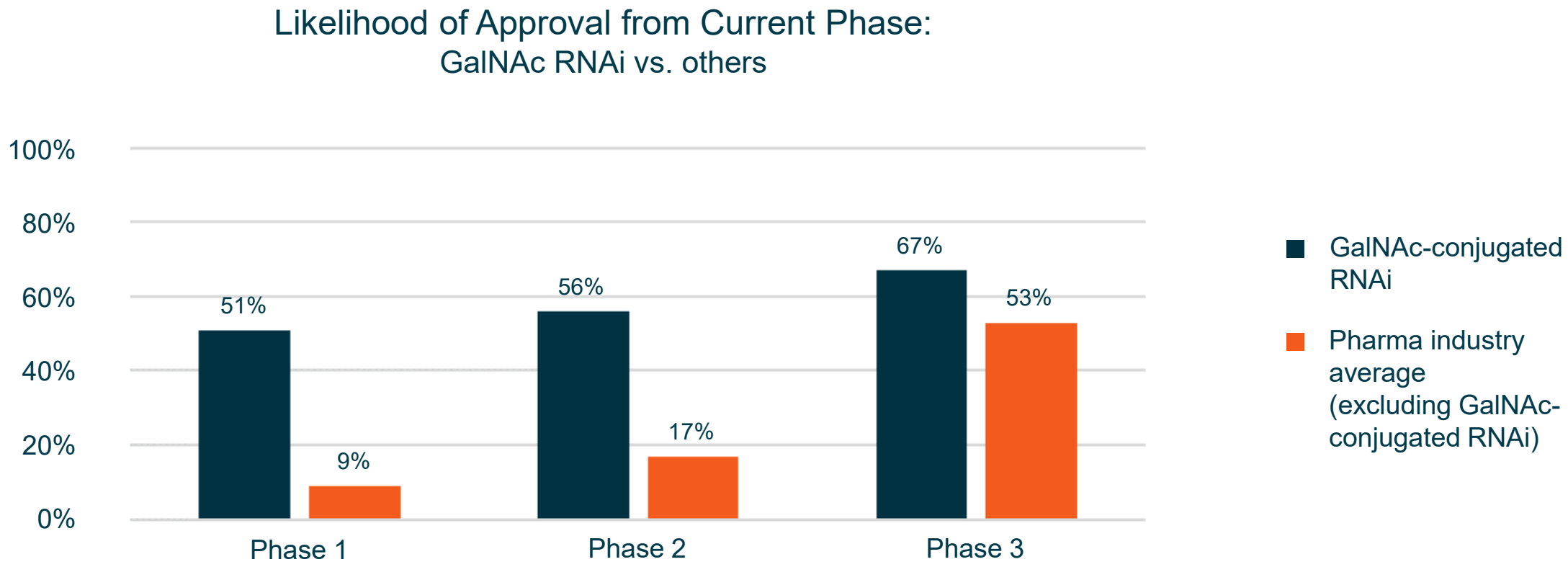


Opportunity to identify new siRNAs targeting many of the remaining 99% (~14,000) of liver-expressed genes

Assuming only 1-2% of remaining genes are targetable, that is still another 140-280 new programs

Source: Human Protein Atlas, GlobalData

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 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

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

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.

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

SLN360

Lp(a) Lowering Program



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 through lifestyle changes or approved medicines
- 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

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

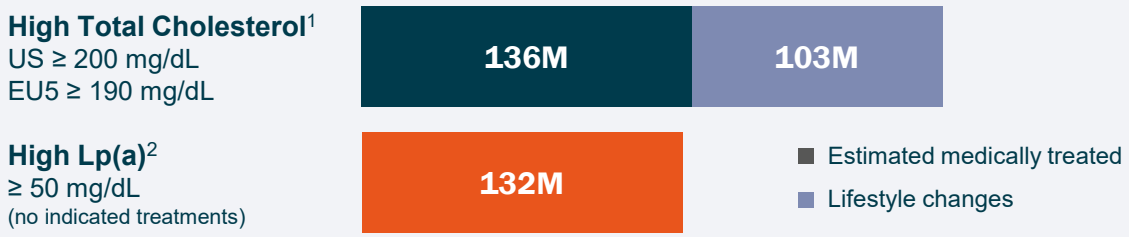
High Lp(a) is a Genetic Risk Factor

- 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



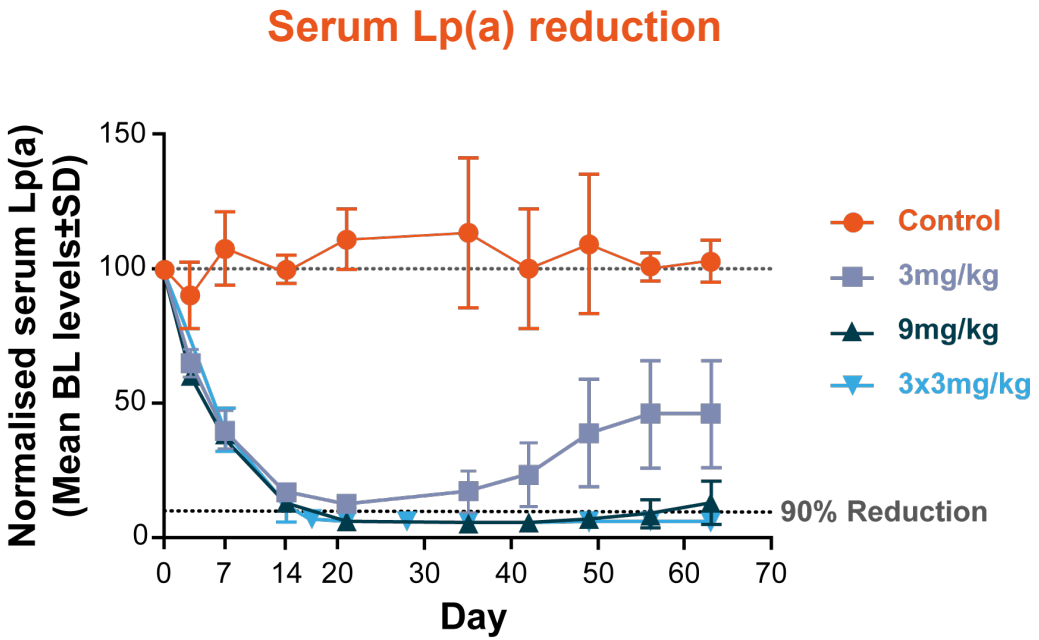
Blockbuster Potential

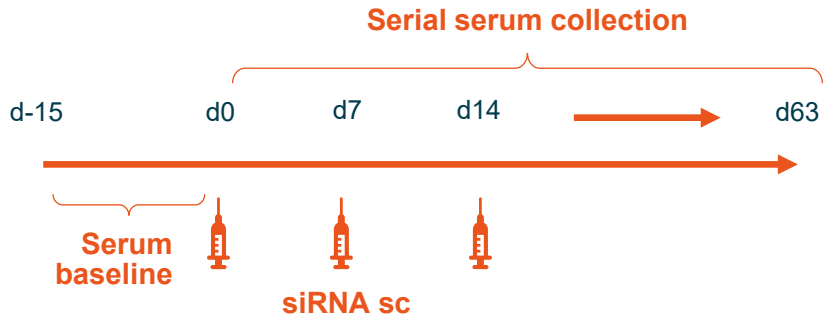
Sales of Cholesterol-Lowering Drugs Peaked at >$30B[3,4]

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





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 and kidney with no detected off target effects

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)
Single Dose Cohorts	8 subjects per cohort (6 active, 2 placebo), up to 5 cohorts
Multiple Dose Cohorts	12 subjects per cohort (9 active, 3 placebo), up to 4 cohorts
Dosing	30 mg, 100 mg, ≤ 300 mg, ≤ 600 mg
Population	Up to 88 subjects total with high Lp(a) ≥ 60 mg/dL

APOLLO

Data from single dose portion expected in Q1 2022

PD = Pharmacodynamics; PK = Pharmacokinetics

Current Status of SLN360 Phase 1 Program

Milestones

- Single dose Cohorts 1-4 enrollment complete; Results expected Q1 2022
- **Independent safety review committee recommendations:**
  - **Established dose range and can proceed to multiple dose portion (no need for Cohort 5)**
  - **Extend follow-up of single dose cohorts from 150 to 365 days**

Strategy

- **Single dose data drives ASCVD phase 2 start in 2H 2022, subject to regulatory discussions**
- Dose and interval can be predicted from single dose data
- Multiple dose provides early safety assessment in our phase 2 ASCVD population

ASCVD = Atherosclerotic Cardiovascular Disease

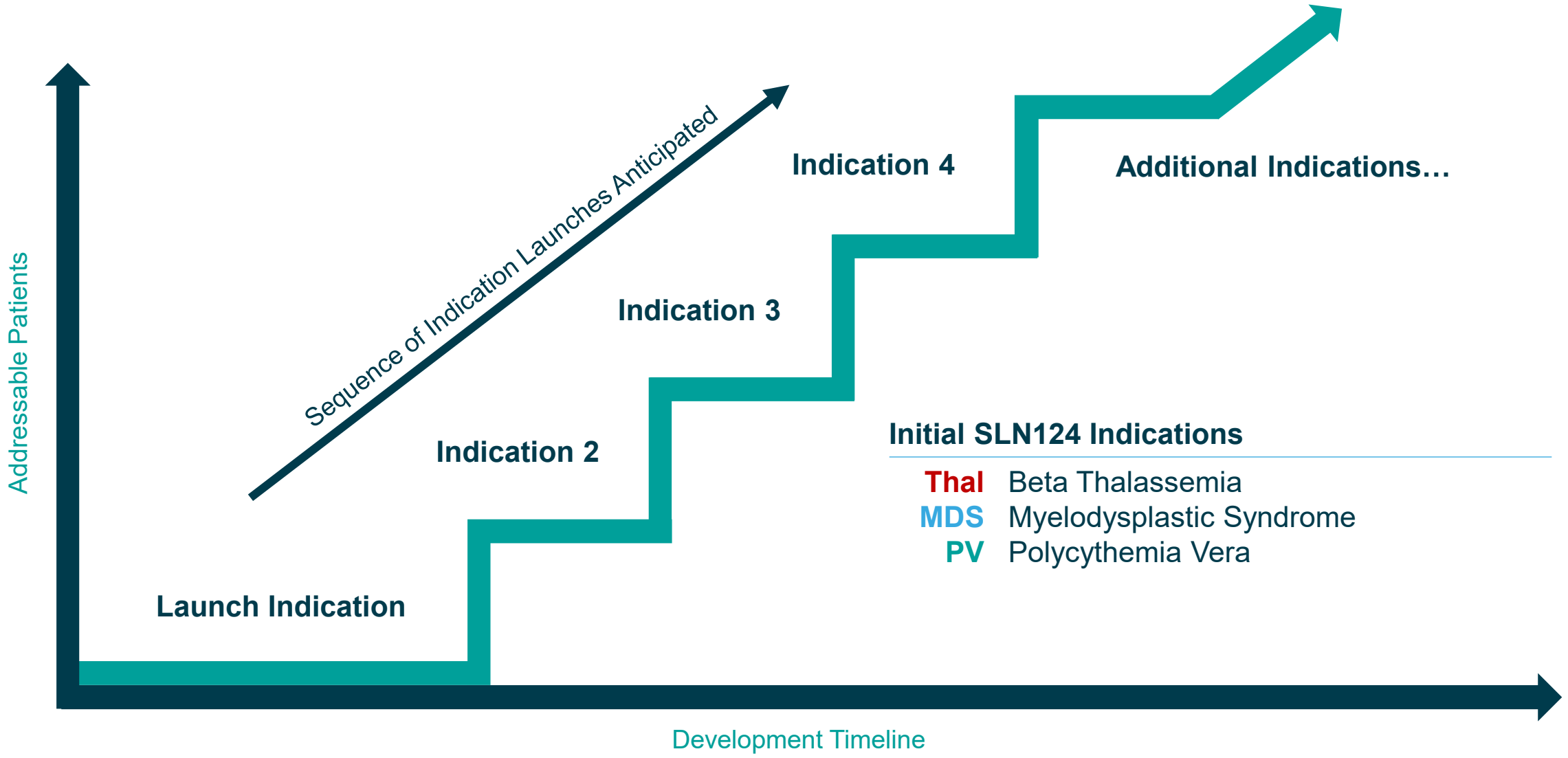


SLN124

Hepcidin Regulation Program

We see SLN124 as a Hematology Franchise Opportunity

With the potential to reach several patient groups in indications with high unmet need



PV Represents a Substantial New Opportunity

Polycythemia Vera

Prevalence
44-57/100,000[1]

~150,000*

~3.5m*

Incidence
The annual incidence of PV is between 1-3/100,000.[2]

Myelodysplastic Syndrome

Prevalence
20/100,000[3,4]

~70,000

~1.5m

Incidence
The annual reported incidence of MDS is ~5/100,000 (age adjusted).[3]

Beta Thalassemia

Prevalence
1/100,000[5,6,7]

~5,000

~100,000

Incidence
Over 40,000 infants are born with Beta Thalassemia each year.[7]

*Using 44/100,000

US Population: 333m, global population: 7,800m

[1] Mehta, J. et al. Leukemia & Lymphoma (2014); [2] Titmarsh, G. et al. Am J Hematol (2014); [3] Cogle, C. R. Curr Hematol Malig Rep (2015); [4] www.aamds.org/diseases/mds
[5] Galanello, R., Origa, R. Orphanet J Rare Dis (2010); [6] Kattamis, A. et al. Eur J Haematol (2020); [7] Modell, B., Darlison, M., Bull World Health Organ (2008)

SLN124 Key Facts

SLN124 modulates hepcidin, the master regulator of plasma iron in the body

By silencing TMPRSS6, SLN124 enables the body to increase endogenous hepcidin and modulate iron distribution

Strong preclinical data in animal disease models, demonstrating therapeutic potential in different pathologies (i.e., amelioration of anemia, reduction of iron overload or hematocrit control)

Long duration of action of SLN124 combined with favorable safety profile in healthy volunteers

Potential for broad mechanistic mode-of-action approach

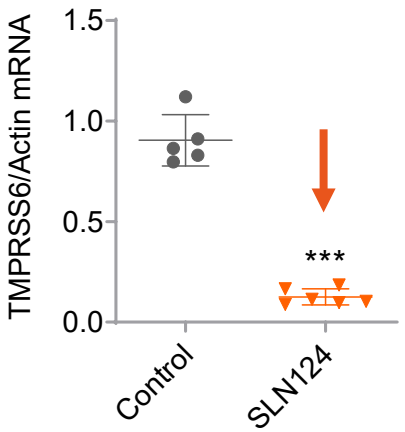
US rare pediatric disease designation for beta thalassemia

Orphan Drug Designation for MDS (US) and beta thalassemia (EU; US)

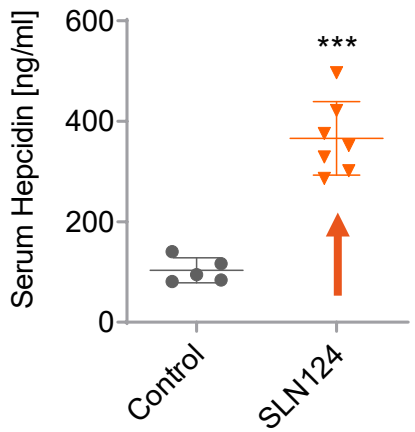
EU = European Union; MDS = myelodysplastic syndrome; US = United States

SLN124 is Designed to Restore Endogenous Hepcidin and Normalize Iron Levels

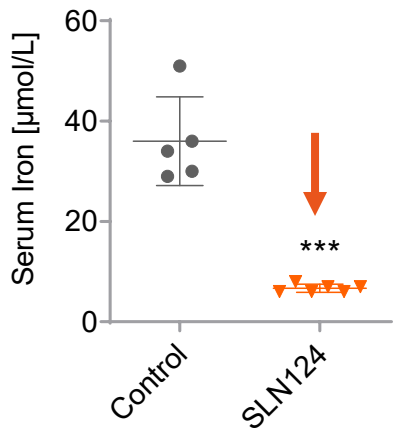
1 Reduces TMPRSS6 in the liver



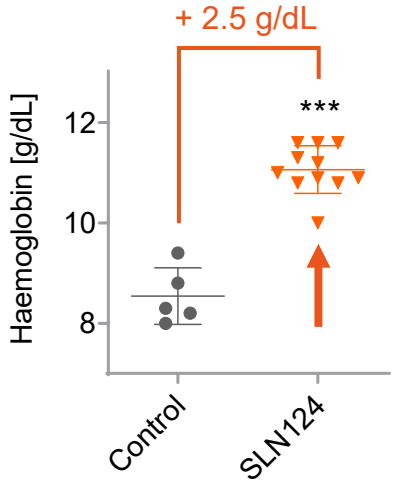
2 Raises endogenous hepcidin



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 dose study
Aim	Investigated the safety, tolerability, PK and PD response of SLN124 in healthy volunteers
Single Dose Cohorts	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

GEMINI

Data presented at ASH 2021

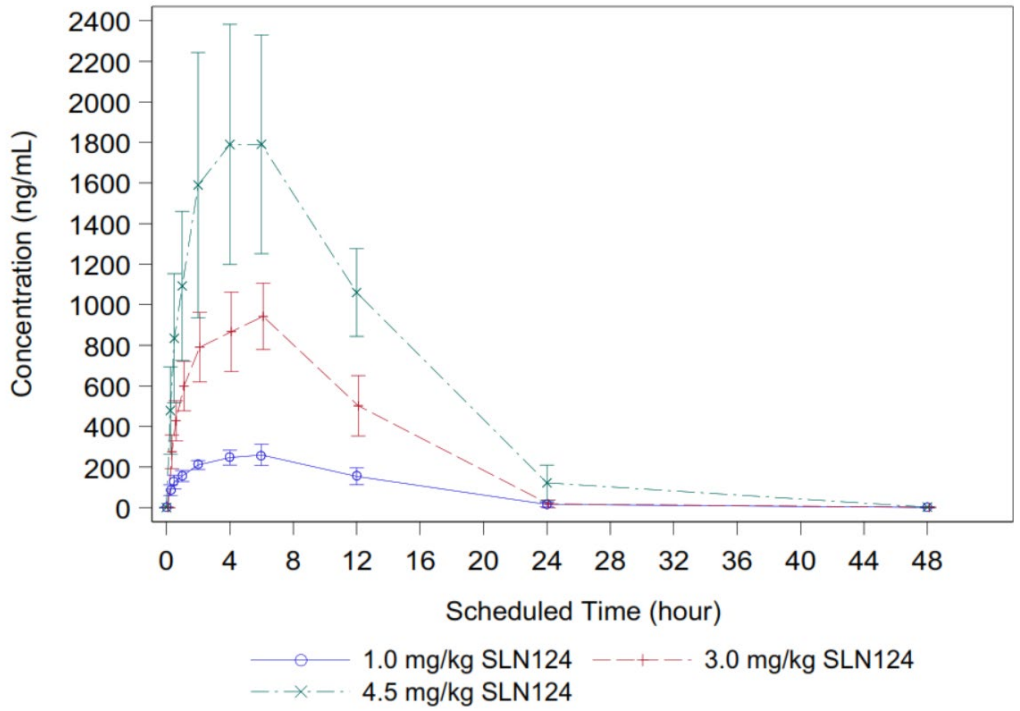
PD: Pharmacodynamics; PK: Pharmacokinetics

SLN124 Demonstrated Strong Safety and Tolerability Profile

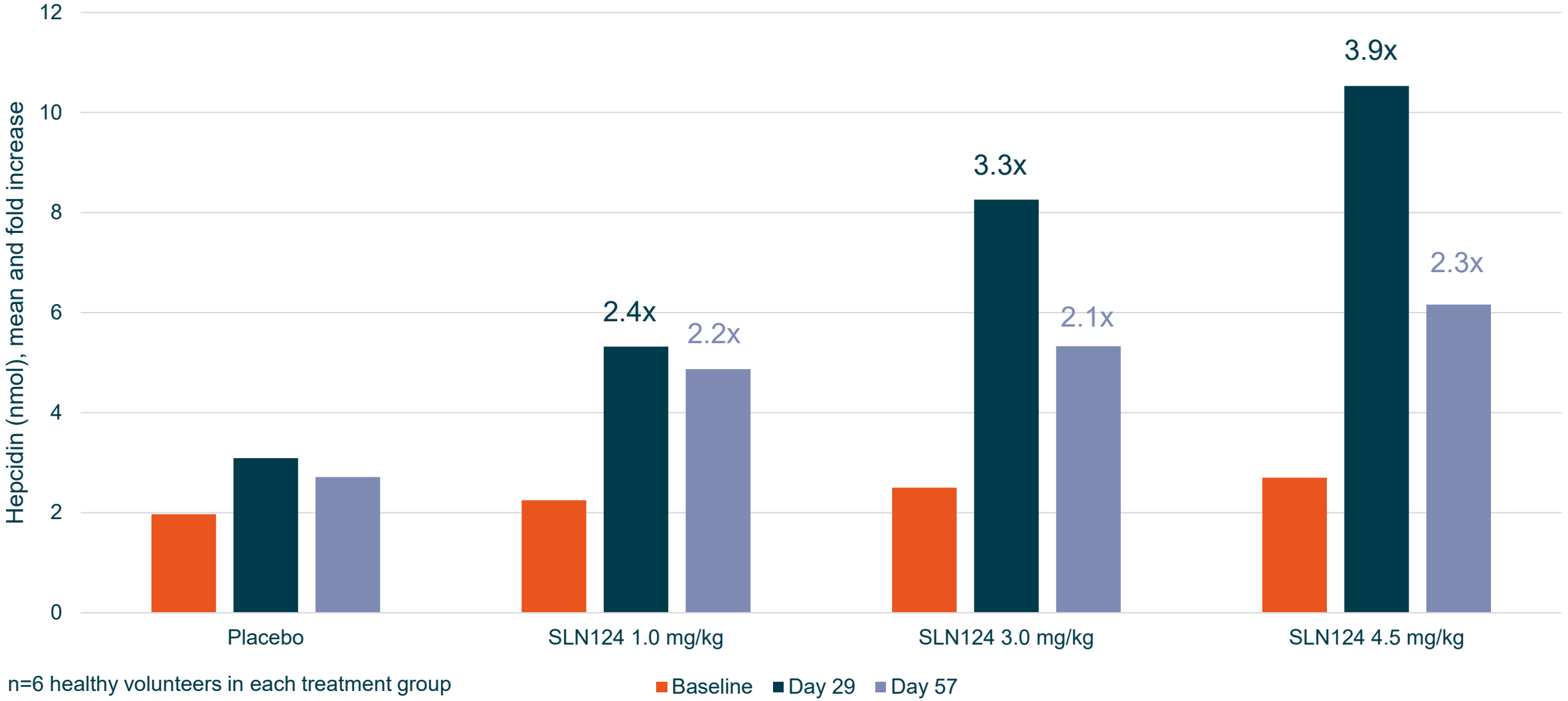
- All 3 dose levels of SLN124 were safe and well-tolerated:
  - No serious or severe treatment emergent adverse events (TEAEs) or TEAEs leading to withdrawal
  - The majority of TEAEs were mild, including transient mild injection site reactions which resolved without intervention

Pharmacokinetic Results

- SLN124 was rapidly distributed :
  - median t_{max} was 4.0 or 5.0 hours
- SLN124 was largely eliminated from plasma within 24-hours post-dose in all dosing groups
- SLN124 plasma concentrations increased in a greater than dose-linear fashion between dosing groups

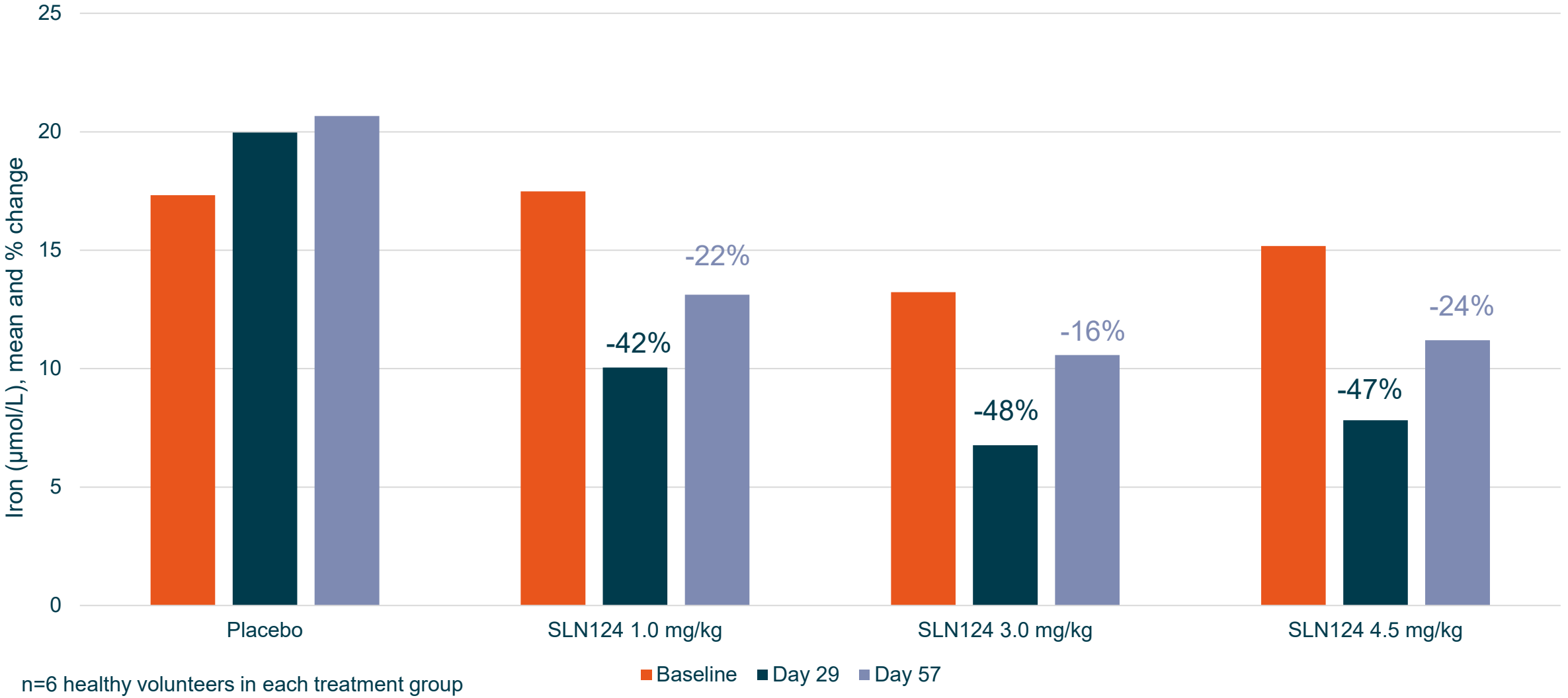


SLN124 Increased Average Hepcidin up to ~4-Fold After a Single Dose with Effect Sustained for ≥ 2 Months



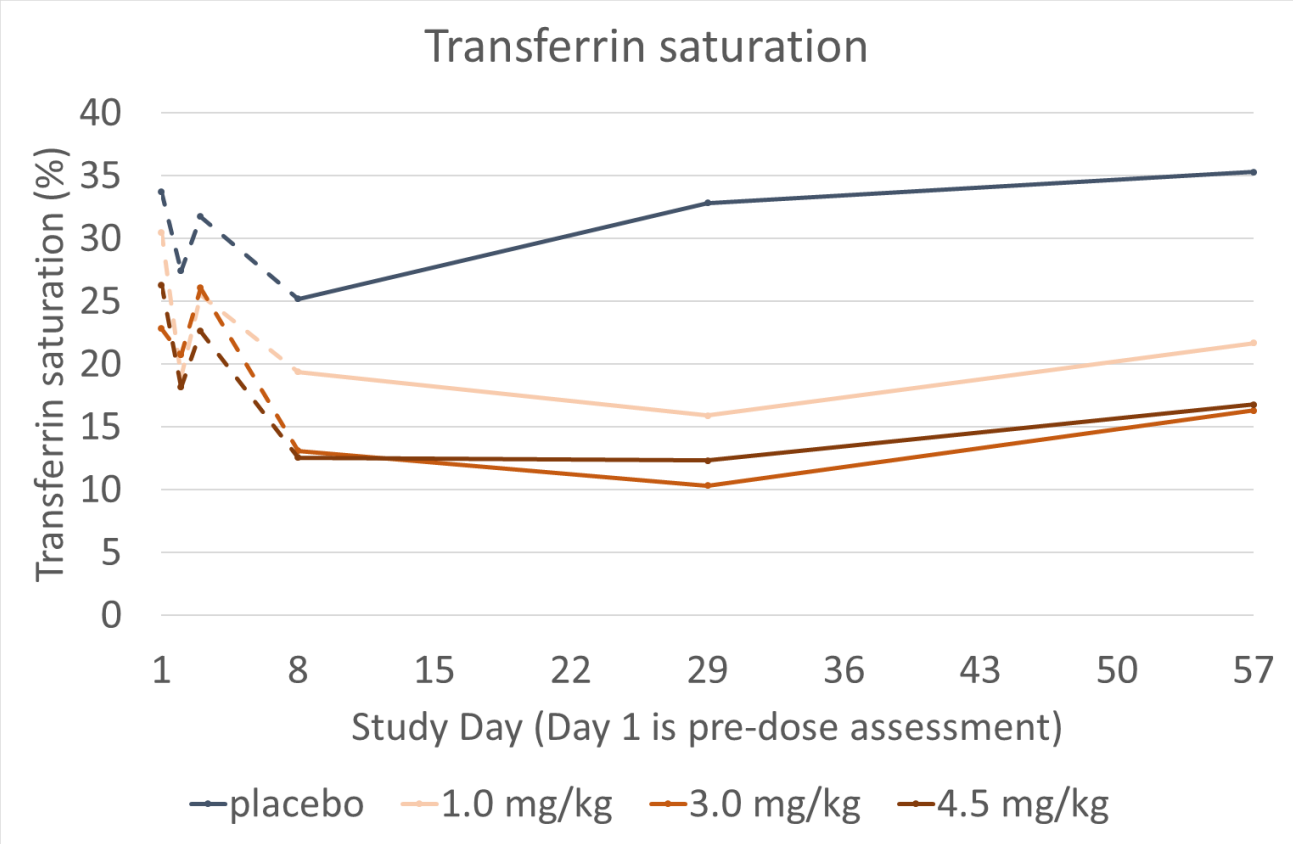
n=6 healthy volunteers in each treatment group

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 Induced Marked Reductions in Transferrin Saturation (TSAT)



- Absolute levels of TSAT achieved (10–16%) are below the level (< 20%) where iron availability to tissue is restricted and at or below that (< 16%) required to support normal erythropoiesis in health

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 well-tolerated
- 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
- Encouraging efficacy signal on serum iron and transferrin saturation and the expected benign safety profile of SLN124 supports further development

SLN124 Phase 1 Program in Adult Thalassemia and MDS

Design	Global, randomized, single-blind, placebo controlled single and multiple dose studies
Aim	Investigate the safety, tolerability, PK and PD response of SLN124 in adults with thalassemia and MDS
Single Dose Cohorts	8 subjects per cohort (6 active, 2 placebo), up to 4 cohorts per study
Multiple 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

Single dose data expected in Q3 2022

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

A Phase 1 study in PV is to be initiated in H2 2022

- **SLN124 Phase 1 study to be initiated in H2 2022**
  - Study Aim: Investigate the safety, tolerability, PK and PD response of SLN124 in patients with polycythemia vera
- **Subsequent development:**
  - Key clinical study endpoints focused on hematological measures
    - i.e. red packed cell volume, cell hemoglobin content, TSAT, hemoglobin
  - Early and late clinical studies use same end-points simplifying development path to approval

PD = Pharmacodynamics; PK = Pharmacokinetics

SLN124 Has The Potential For a Broad Mechanistic Mode-of-Action Approach

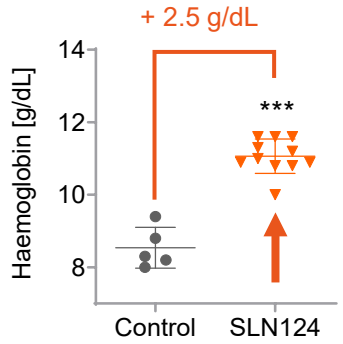
Silencing TMPRSS6 **by SLN124** increases endogenous hepcidin, with potential beneficial effects in several hematological disorders.

SLN124 → **Reduce TMPRSS6** → **Increase endogenous hepcidin** → **Decrease NTBI**

- **Inhibit iron accumulation**
- **Restrict iron to erythropoiesis**

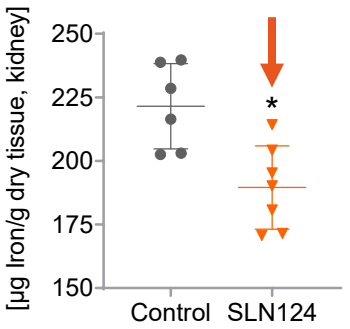
***Iron loading anemias** (e.g. beta thalassemia, MDS)* → **Reduce anemia**[1]

Vadolas et al. 2021 Br J Haematol. PMID: 33942901



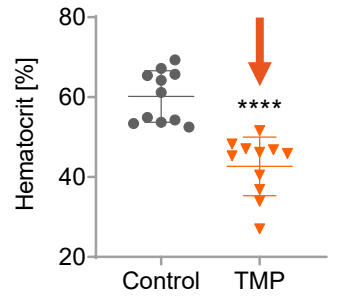
Hereditary hemochromatosis → **Prevent iron overload**[2]

Altamura et al., HemaSphere 2019 (PMID 31976476)



Polycythemia vera → **Reduce red packed cell volume**[3]

Presented at EHA 2021



NTBI = non-transferrin-bound iron; Studies performed in a rodent model for 1: beta thalassemia ($Hbb^{th3/+}$), *** p≤0.001; 2: hemochromatosis ($Hfe^{-/-}$), * p≤0.05; 3: polycythemia vera, **** p≤0.0001

2021 Key Accomplishments

SLN360 Lp(a) Lowering Program

- Completed enrollment in phase 1 SD study
- Key takeaways from independent safety review committee meeting:
  – Extended follow-up period in SD study from 150 days to 365 days to fully assess the duration of action
  – Established therapeutic dose range for MD study

SLN124 Hepcidin Regulation Program

- Presented positive data in SLN124 healthy volunteer study – first clinical data from **mRNAi GOLD™** platform
- Started dosing patients in two phase 1 SD studies for thalassemia and MDS
- Positive preclinical data in PV

Partnered Programs

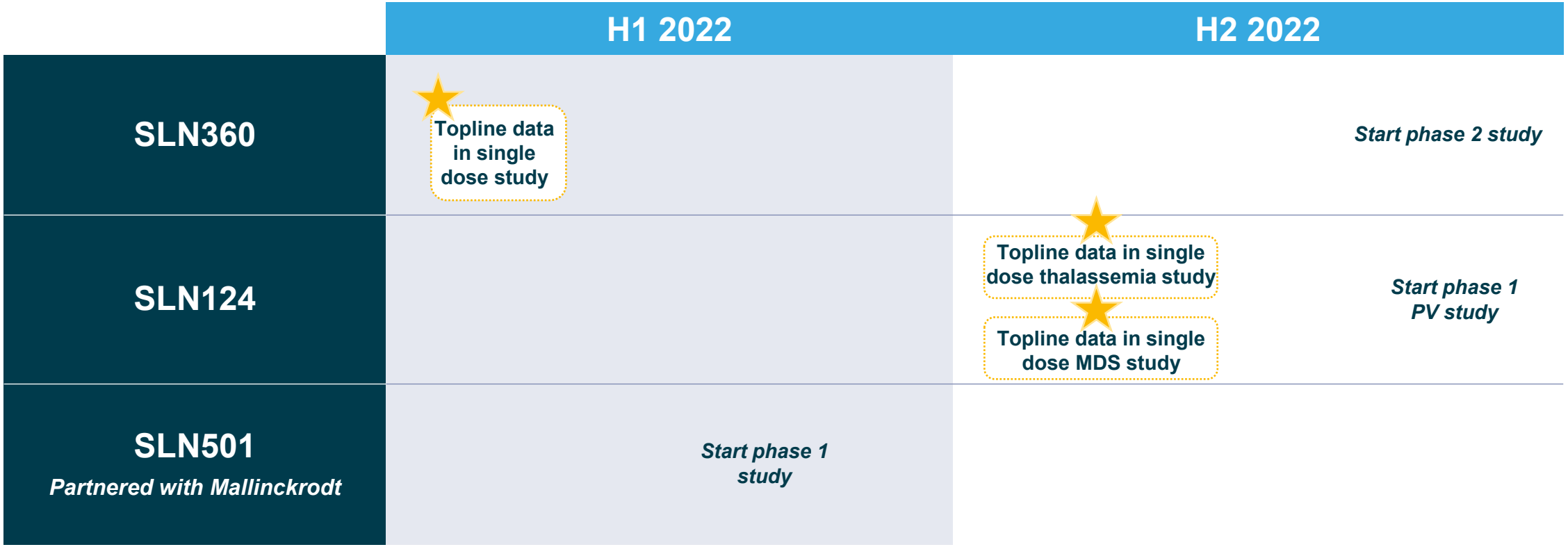
- Started work with AstraZeneca on second target
- Started work with Mallinckrodt on third complement target and initiated IND enabling studies for SLN501
- Secured new collaboration with Hansoh Pharma

Corporate/Financial

- On-track for 2-3 INDs per year from 2023
- Growing interest from top US healthcare funds combined with non-dilutive capital from collaborations
- Completed AIM delisting process in November 2021 and now exclusively trading on the Nasdaq

Major Clinical Milestones Anticipated in 2022

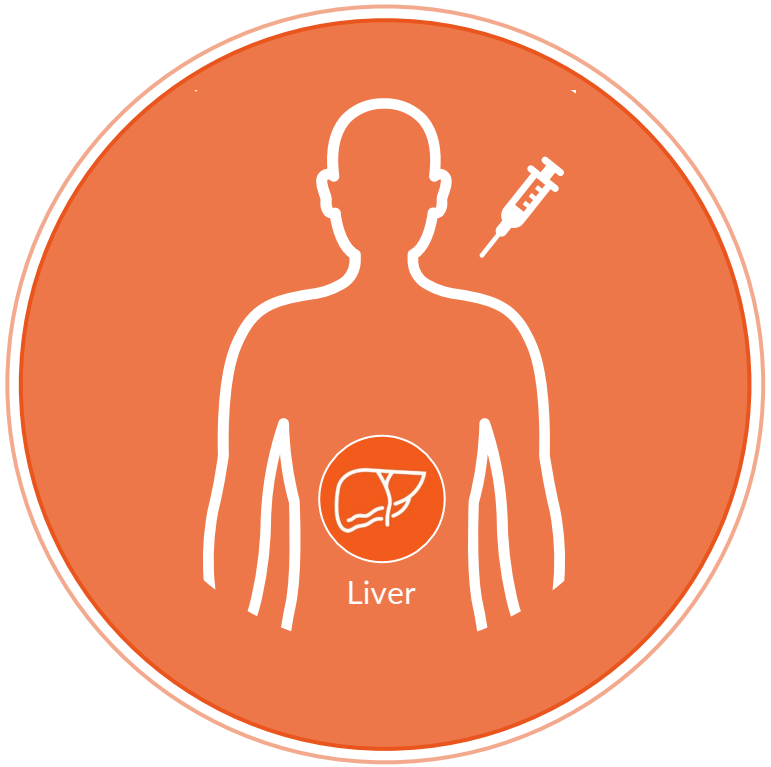
Topline data in SLN360 study anticipated this quarter



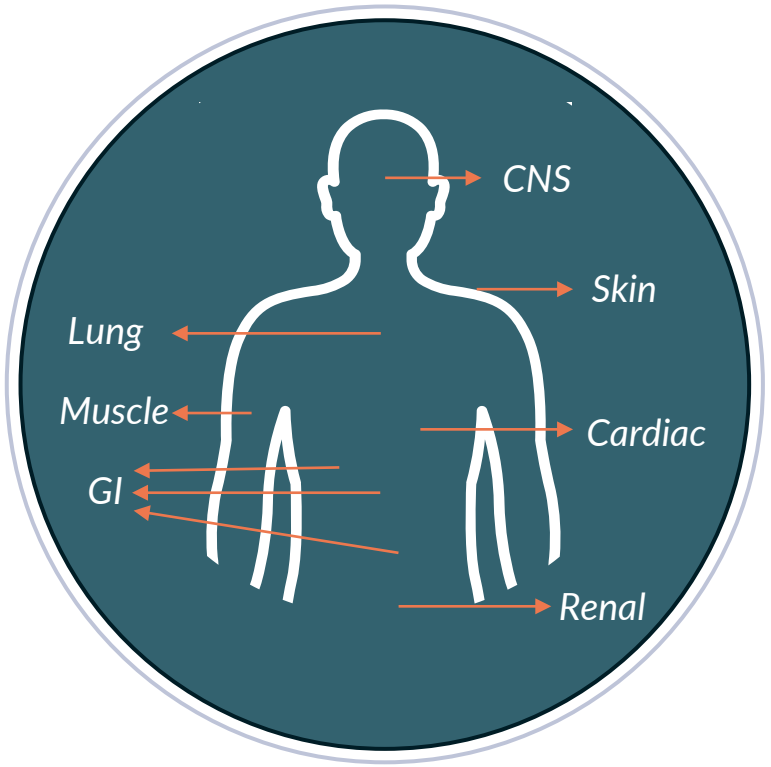
Note: all programs are at potential risk of delay due to COVID-19

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: Nasdaq	
Stock Price (1/4/22)	$23.78
Common Shares Outstanding (9/30/21)	89,777,000
Market Capitalization (1/4/22)	~£525m /~$712m
Cash (9/30/21)	£76.5m
Debt	$0

Note: Silence announced Hansoh Pharma collaboration in October 2021. The deal provided a $16 million upfront cash payment to Silence.