SILENCE THERAPEUTICS

Silence Therapeutics

# Corporate Presentation

August 2021

# Forward-Looking Statements

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# Poised for Transformation

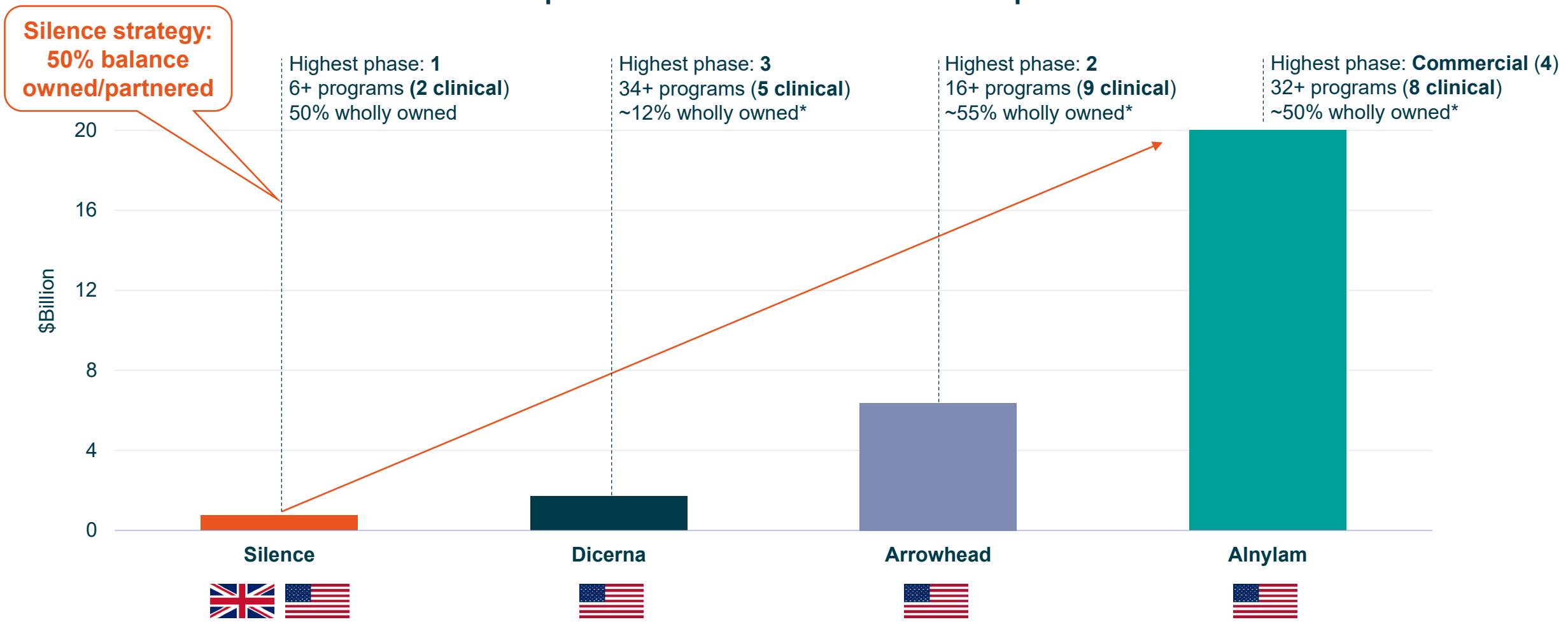
## Major Clinical Data Readouts in Wholly Owned Programs Combined with Rapid Discovery Pipeline Growth

| | |
|---|---|
| **Pioneers in RNAi** | • Two decades of know-how combined with robust and growing IP estate<br>• 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<br>• Advancing two proprietary phase 1 clinical programs<br>  ◦ SLN360 targeting high and prevalent unmet need in cardiovascular disease due to high lipoprotein(a)<br>  ◦ 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<br>• Anticipate 2-3 INDs per year from 2023 (proprietary and partnered programs)<br>• Significant opportunity to address disease causing targets in the liver |
| **Strong Financial Position** | • £81.2m at the end of June 2021<br>• AIM and Nasdaq listed (SLN) - market cap ~£544m /~$754m* |

* Market Capitalization as of August 10, 2021

# We believe the Path to Value Creation is Clear

## Market capitalization of established RNAi companies




Market Capitalization as of August 10, 2021;
Programs include discovery phase through to marketed drugs, disclosed on company website and presentations 2Q 2021. *internal analysis

# 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

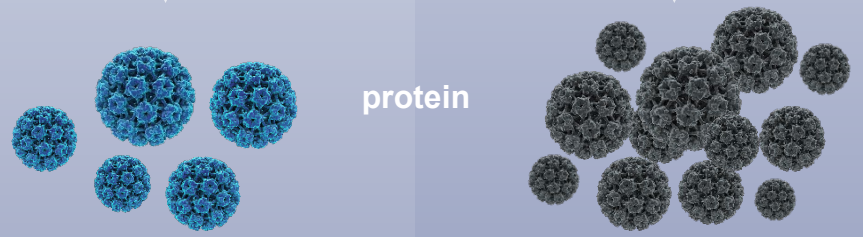



The information in DNA is transcribed into messenger RNA (mRNA)



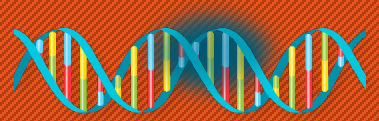

Abnormal DNA message is carried into resulting mRNA

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



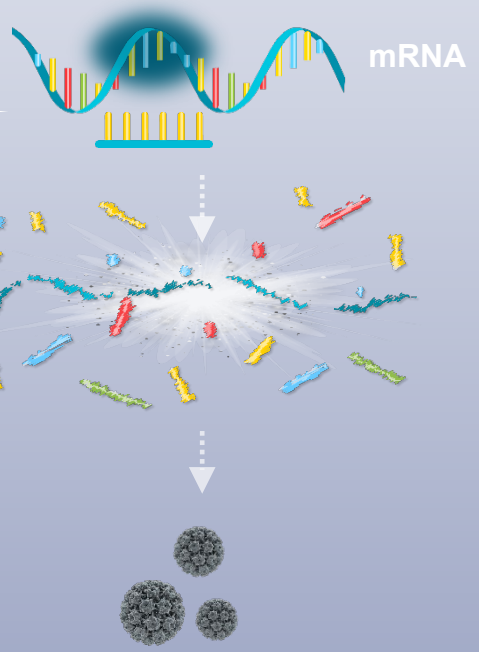
Mutated DNA

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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

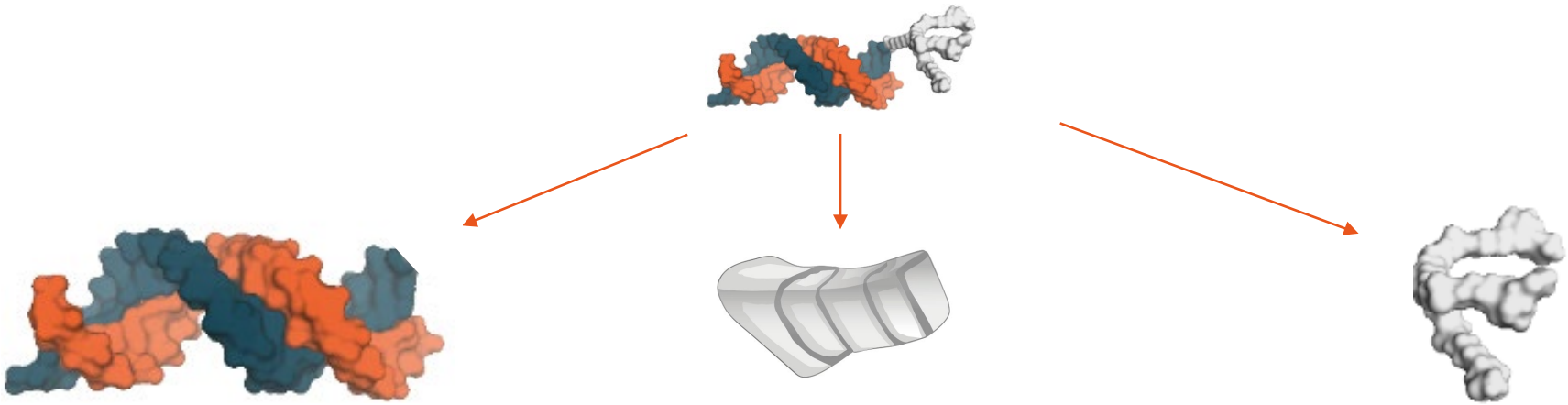
## Durable

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 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

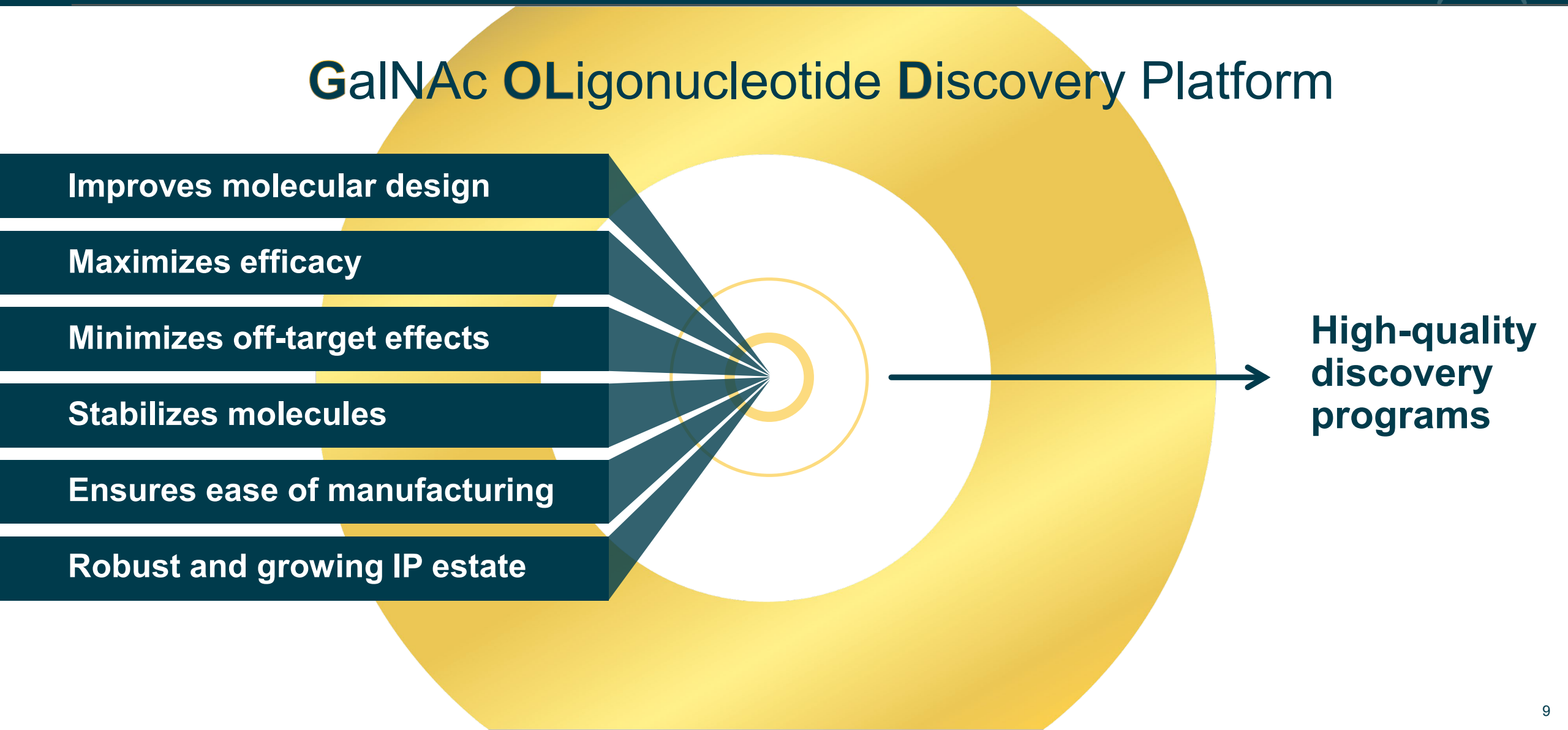
(delivery tool)

- 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

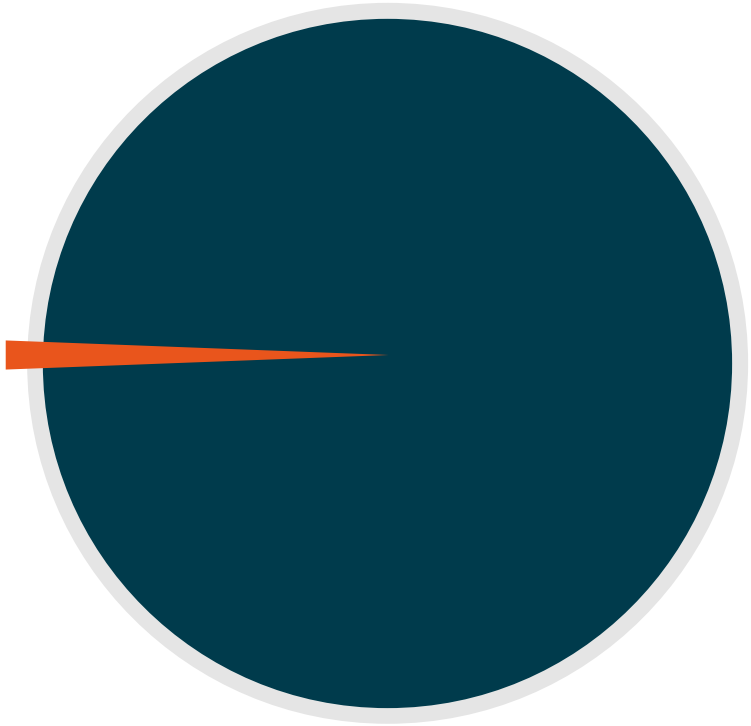
## GalNAc OLigonucleotide Discovery Platform



# 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

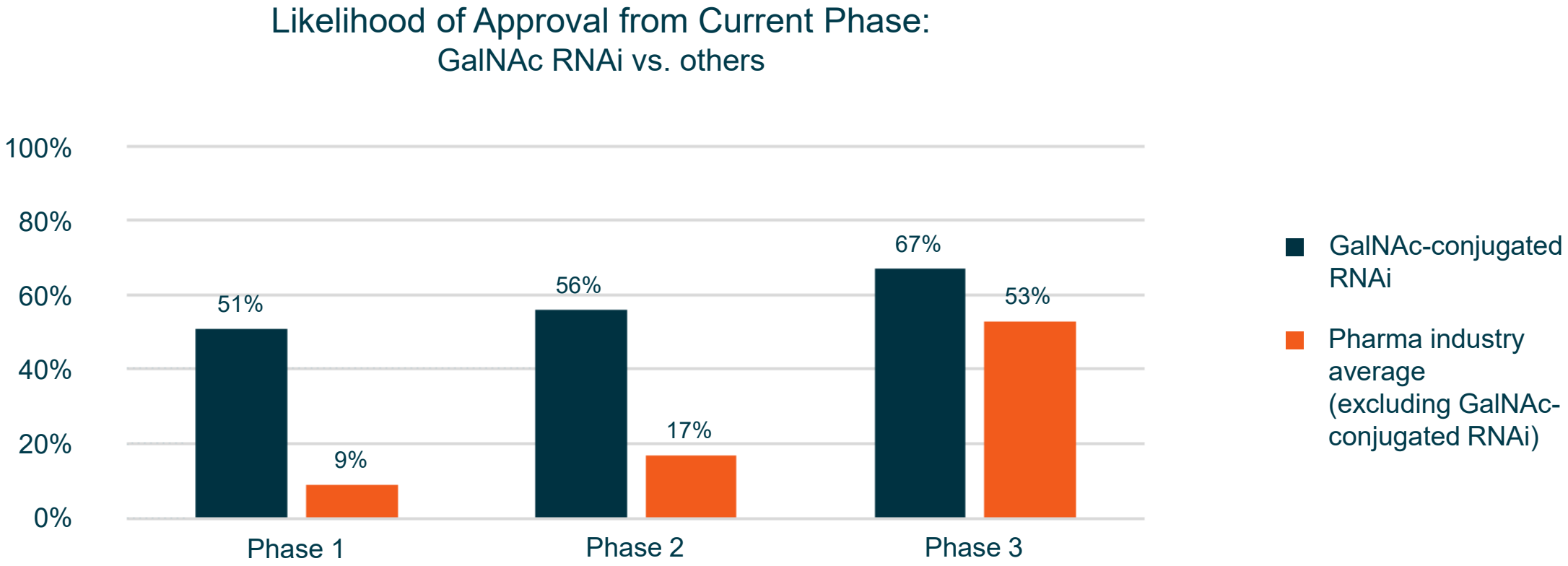
- **High-quality target identification** using translational genomics
- **Lower attrition rates** in discovery enabled by machine learning
- **GalNAc strategic partnerships** to enhance pipeline opportunities (e.g. target selection)

**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

| | H2 2021 | H1 2022 | H2 2022 |
|---|---|---|---|
| **SLN360** | ✓ Fully enrolled 4 cohorts of APOLLO single-ascending dose study in healthy subjects with high Lp(a) | ★ Topline data from APOLLO single-ascending dose study (4 cohorts) | |
| **SLN124** | ★ Present more data from GEMINI healthy volunteer study | | ★ Topline data from GEMINI II single-ascending dose studies in thalassemia and MDS |

**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



# 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**

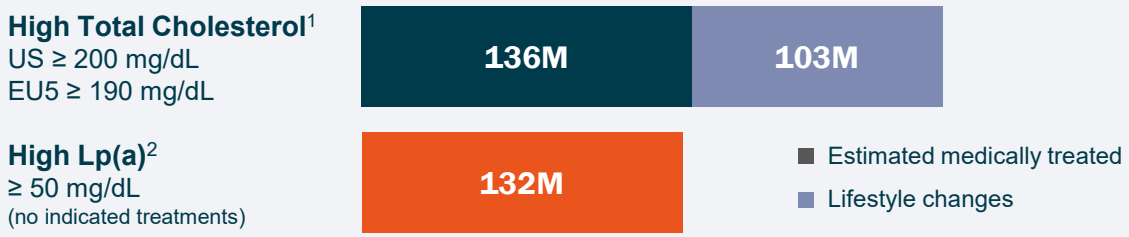
**High Lp(a) is a Genetic Risk Factor**

- 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



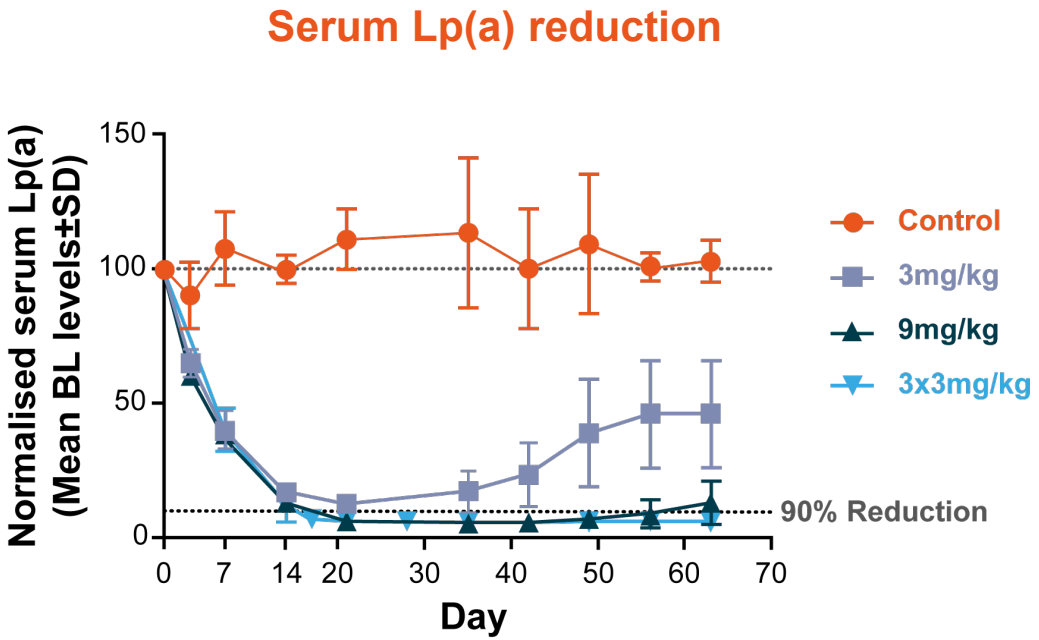

## Blockbuster Potential

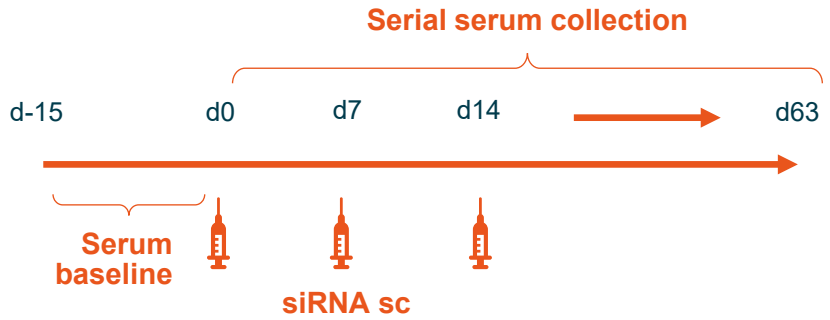
Sales of Cholesterol-Lowering Drugs Peaked at >$30B[3,4]

| **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




| 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)

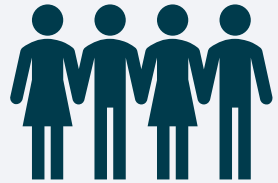
## MYELODYSPLASTIC SYNDROME (MDS)

**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)



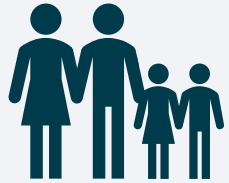
## THALASSEMIA

**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

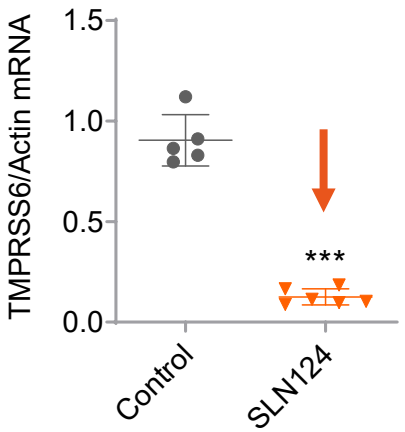
- A rare genetic blood disorder that affects children and adults
- The majority are dependent on regular blood transfusions (TDT), while others are transfused less frequently (NTDT)
- Severe limitations and low quality of life with current treatments
- Opportunity to improve quality of life by reducing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



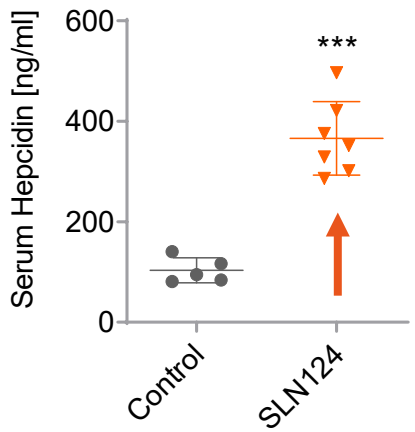
[1] Internal analysis; [2] Kattamis et.al, Eur J Haematol. 2020;105:692; TDT: transfusion-dependent thalassemia; NTDT: non- transfusion-dependent thalassemia

# SLN124 is Designed to Restore Endogenous Hepcidin and Normalize Iron Levels

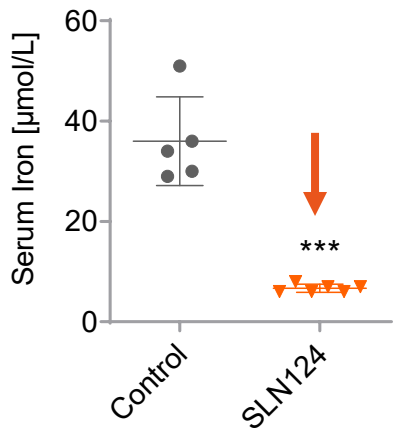
**1** Reduces TMPRSS6 in the liver



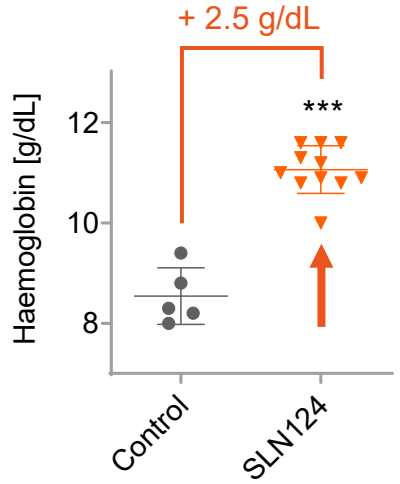

**2** Raises endogenous hepcidin




**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 |

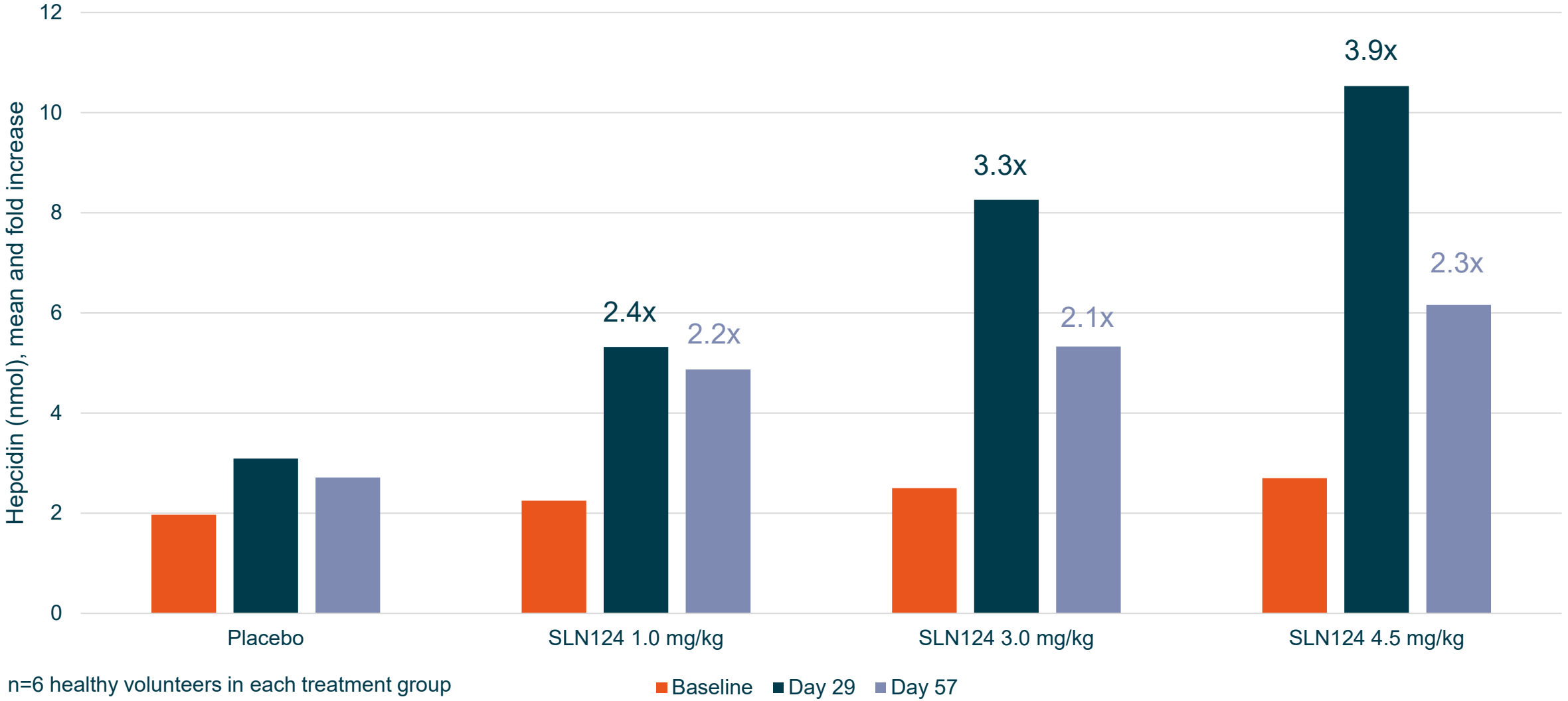



PD: Pharmacodynamics; PK: Pharmacokinetics

# Positive Results from SLN124 Healthy Volunteer Study

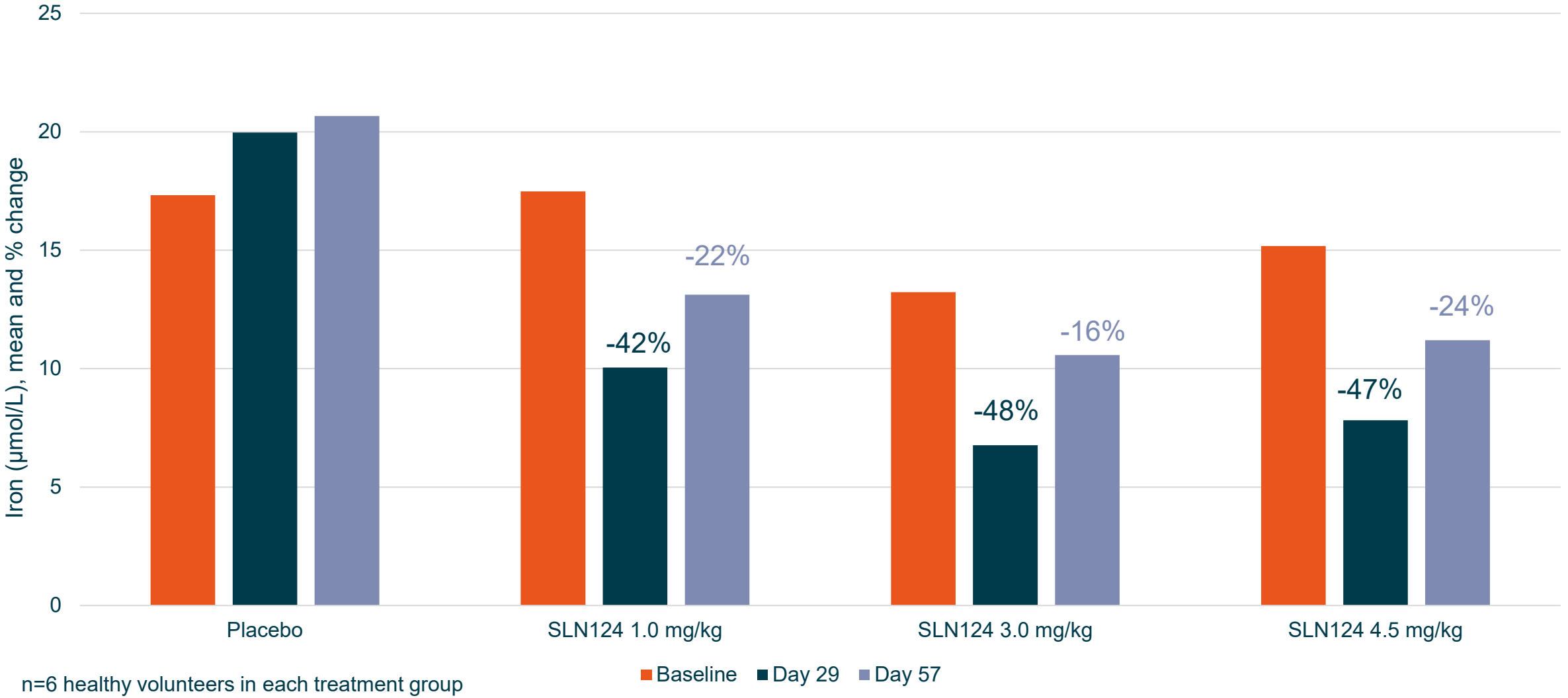
- First clinical data from **mRNAi GOLD™** platform
- Demonstrated proof of mechanism for SLN124
- All 3 dose levels of SLN124 were safe and generally well-tolerated
  - No serious or severe treatment emergent adverse events (TEAEs) or TEAEs leading to withdrawal
  - Majority of TEAEs were mild, including 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

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[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

Mallinckrodt

**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)

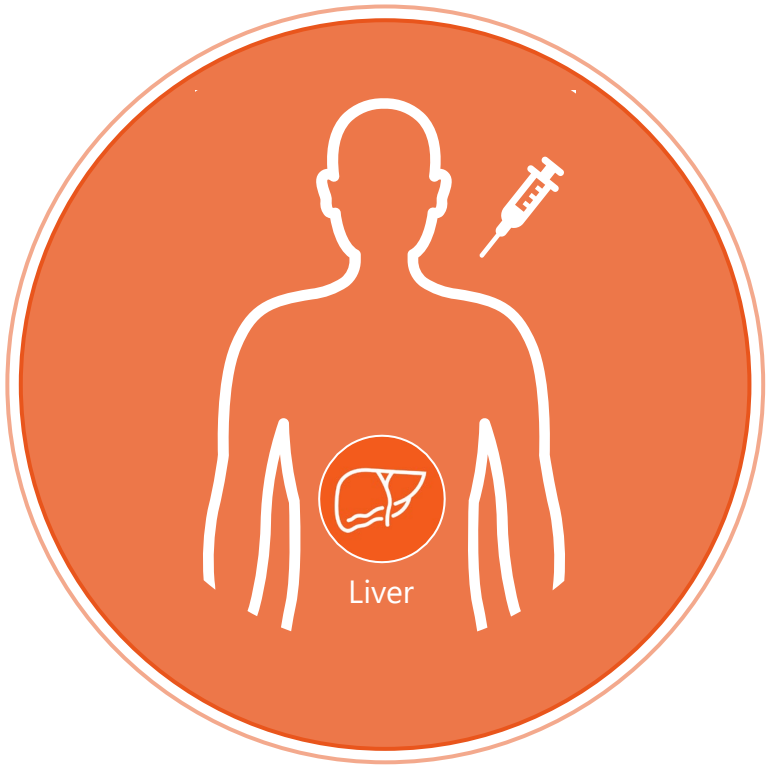
Takeda

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

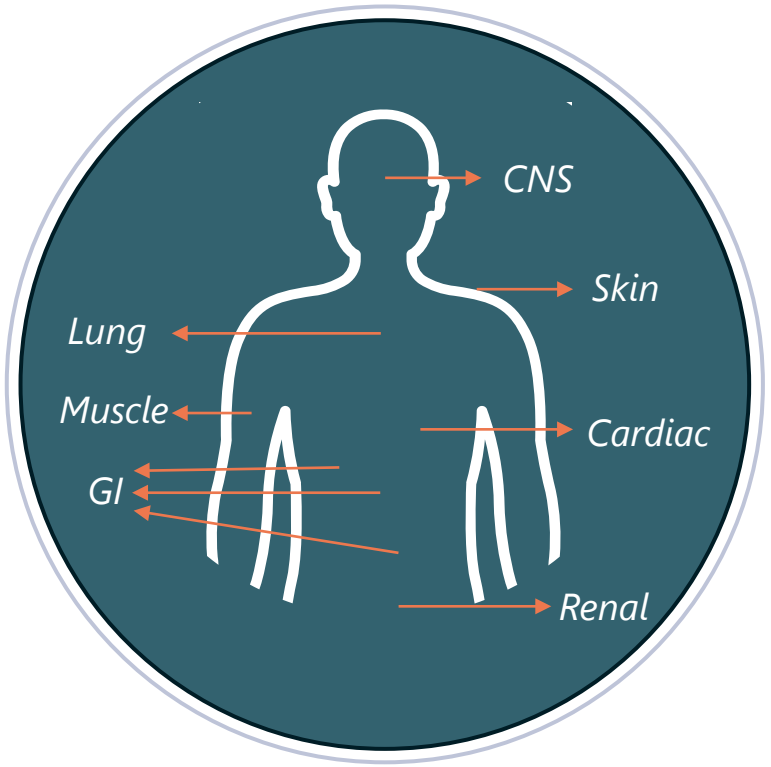
[1] Of the $60m, $20m was paid in May 2020 and a further $40m was paid in H1 2021.

# 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 (08/10/21) | 607p / $25.73 |
| Common Shares Outstanding (6/30/21) | 89,735,448 |
| Market Capitalization (08/10/21) | ~£544m /~$754m |
| Cash (6/30/21) | £81.2m |
| Debt | $0 |