SILENCE THERAPEUTICS

Silence Therapeutics

Corporate Presentation

March 2022

Forward-Looking Statements

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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 Lp(a) Lowering Program** - positive topline data in phase 1 study in healthy volunteers with high Lp(a) • **SLN124 Hepcidin Regulation Program** – positive data in phase 1 study in healthy volunteers • **SLN501 C3 Lowering Program** – phase 1 study with Mallinckrodt planned for H1'22
Proprietary mRNAi GOLD™ Platform	• **Positive clinical data in two programs showing favorable safety/tolerability profiles, robust knockdown of target gene and strong durability of effect after a single dose** • **Leveraging hybrid business model to maximize substantial opportunity in the liver**
Strong Financial Position	• **~$99m / £73.5m at the end of December 2021** • **Nasdaq listed (SLN) - market cap ~$497m / ~£381m***

* Market Capitalization as of March 15, 2022 Lp(a) = Lipoprotein(a)

Multiple Potential Value Drivers in 2022

Positive topline data in SLN360 study - late-breaker at ACC on April 3, 2022

- Single-ascending dose durability data expected in Q3 2022
- Phase 2 ASCVD study planned for H2 2022, 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 planned for H2 2022

SLN501 (complement program with Mallinckrodt) phase 1 study on-track to start in H1 2022

ASCVD = atherosclerotic cardiovascular disease; PV = polycythemia vera

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



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



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. 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

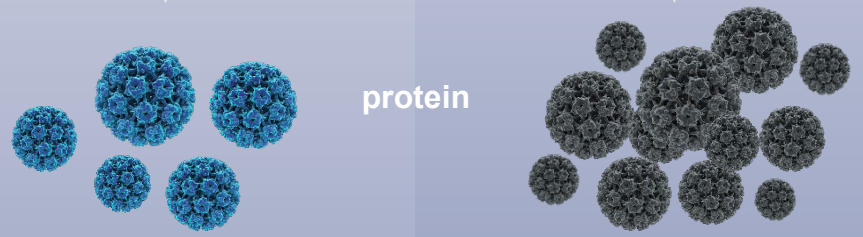


The information in DNA is transcribed into messenger RNA (mRNA)



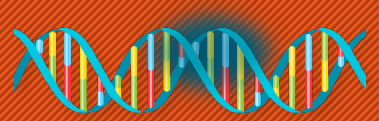
Abnormal DNA message is carried into resulting mRNA

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



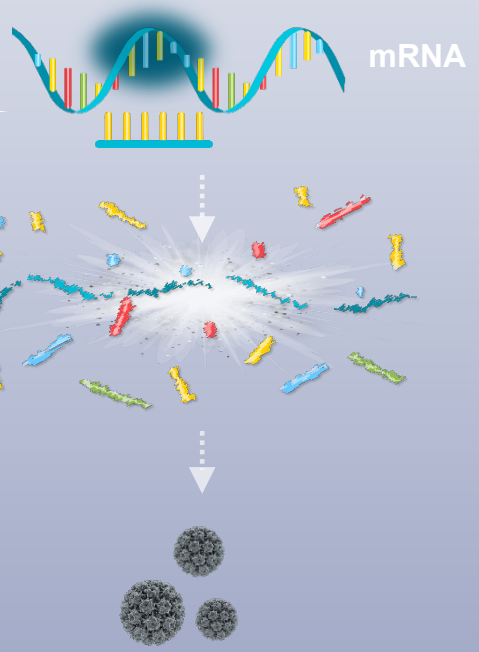
Mutated DNA

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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

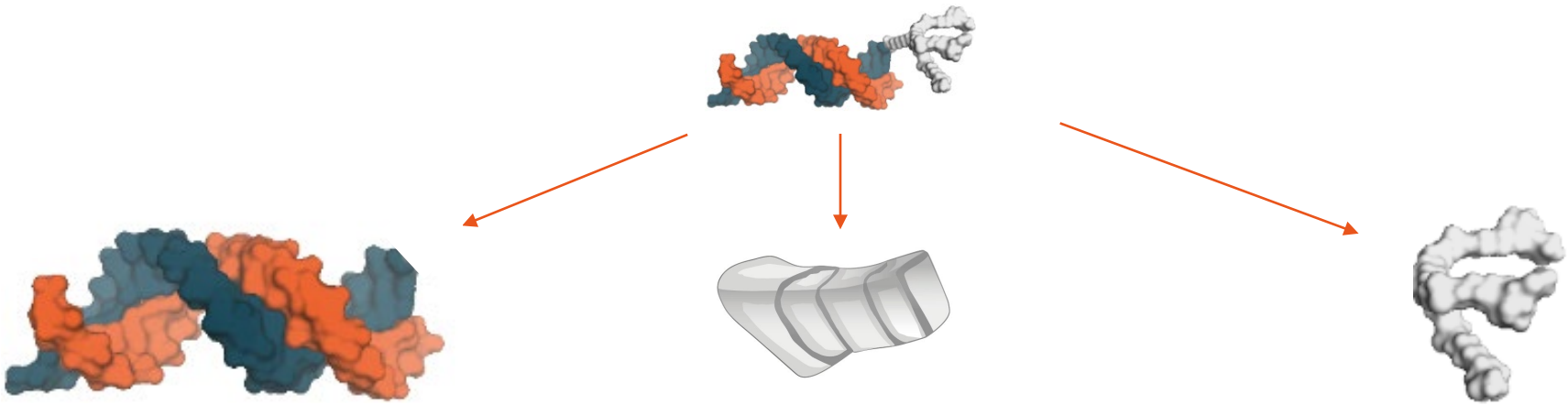
Durable

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

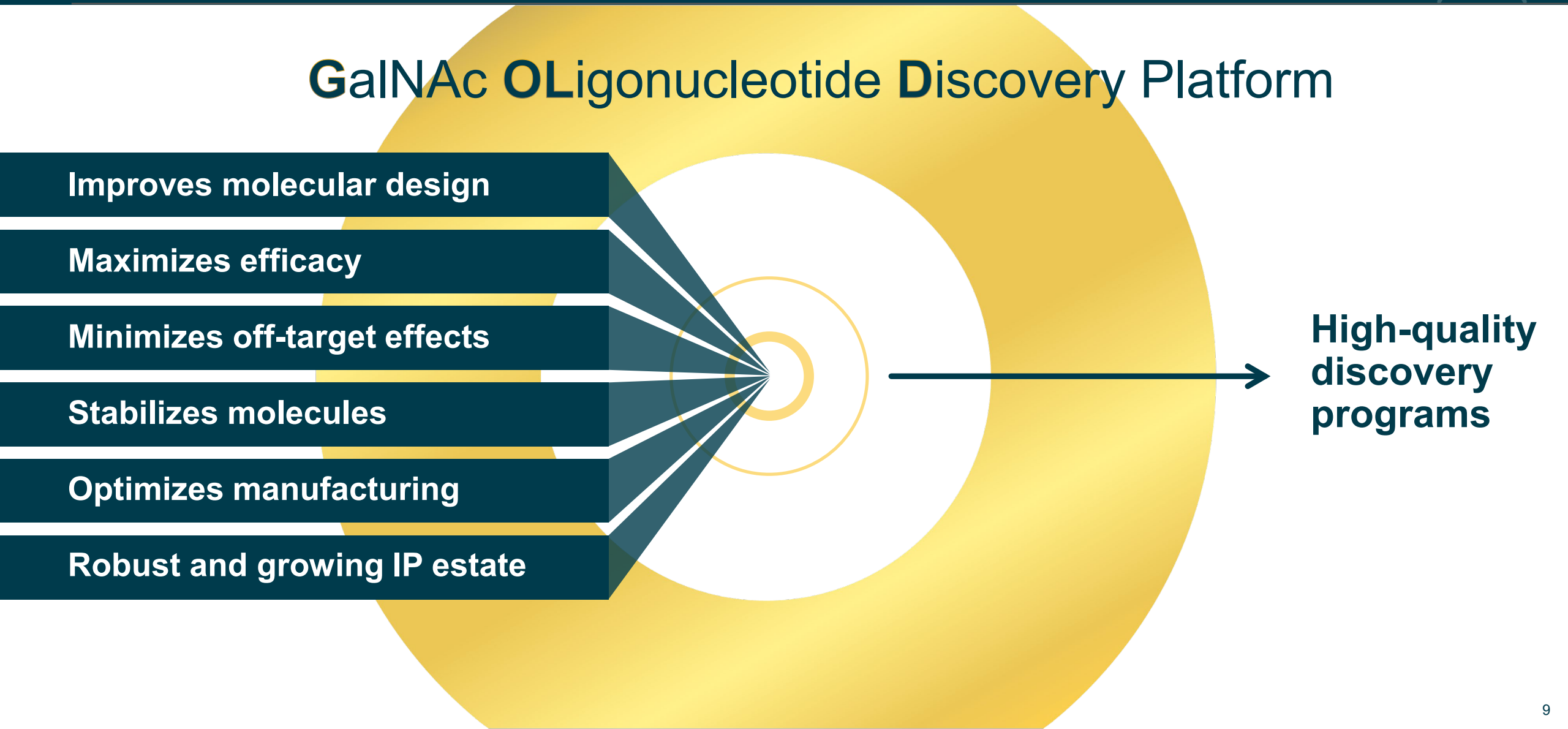
(delivery tool)

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

Continuous Fine-Tuning to Further Improve Performance

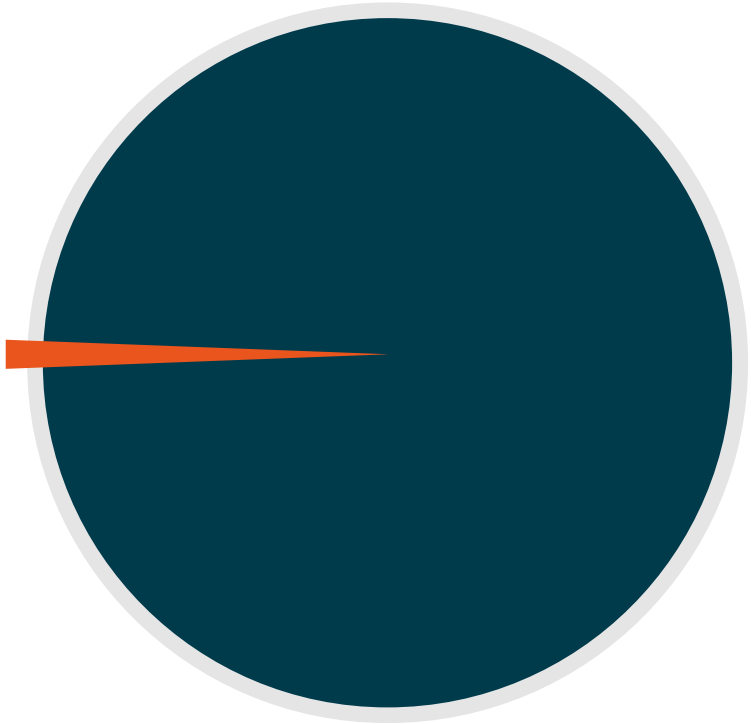
mRNAi GOLD™ Platform Approach: Precision-Engineered Therapies

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

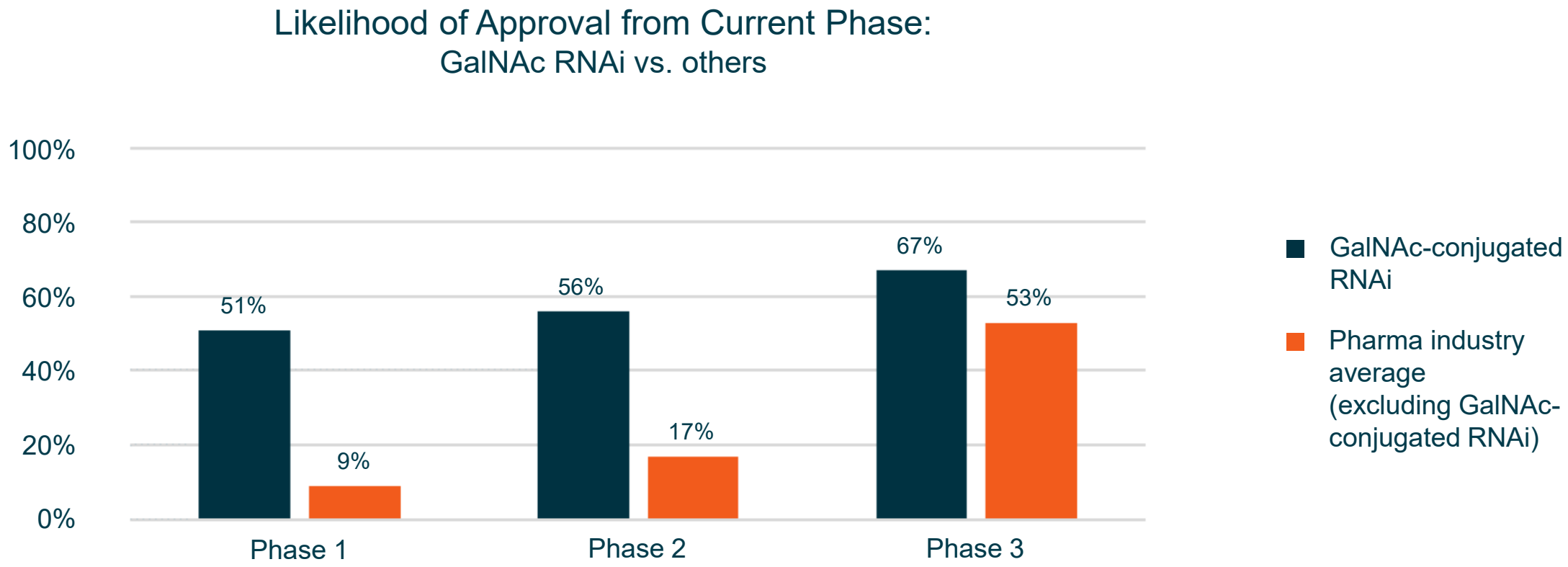


Opportunity to identify new siRNAs targeting many of the remaining 99% (~14,000) of liver-expressed genes

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

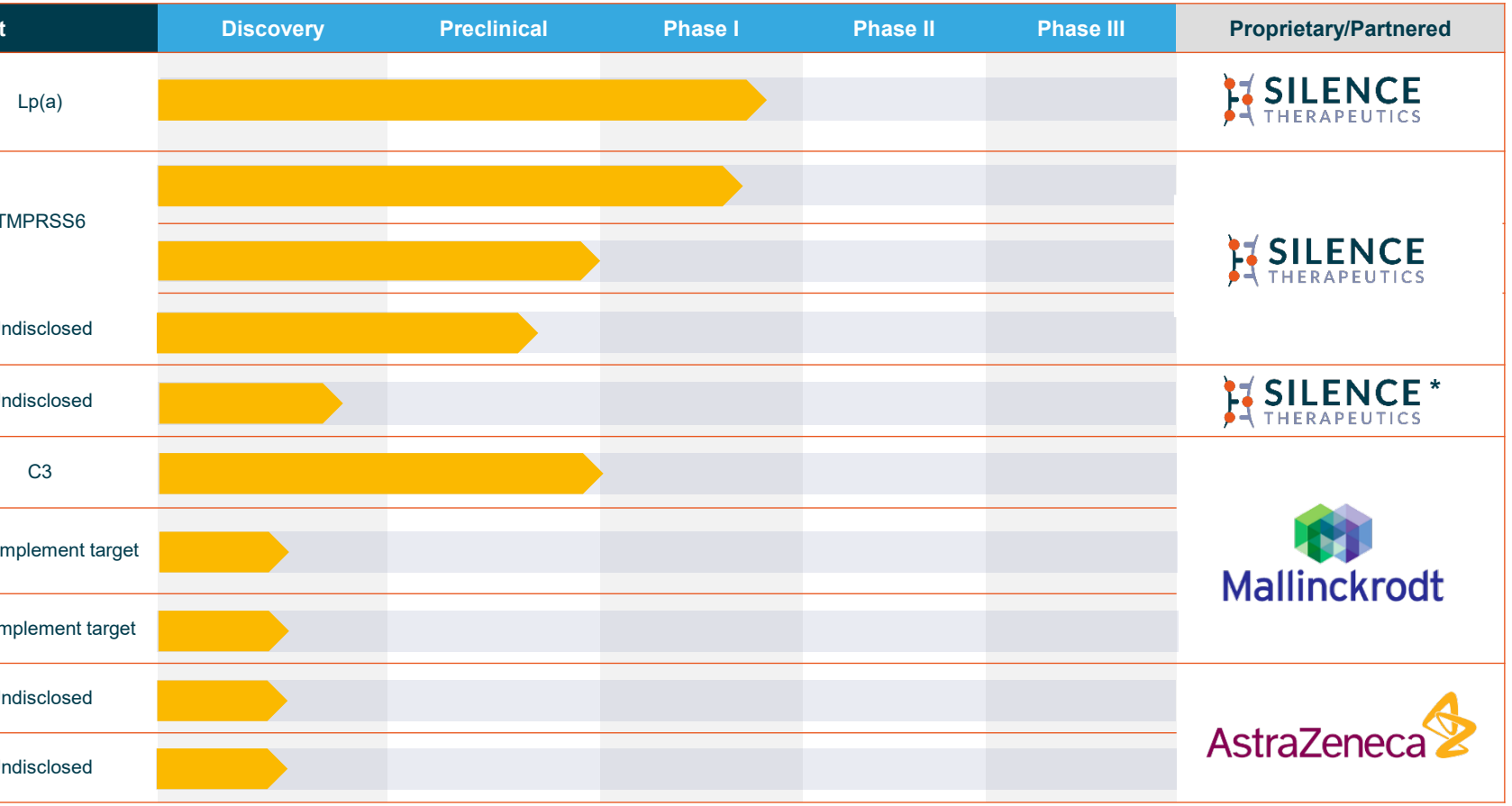
- Upfront cash payment of $20 million and an equity investment of $5 million
- Up to $2 billion in potential milestones plus royalties for 3 targets
- Exercised option to license all 3 complement targets

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.

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

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

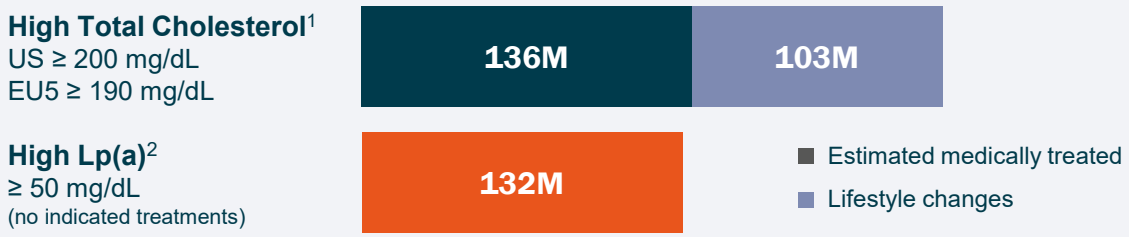
High Lp(a) is a Genetic Risk Factor

- 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



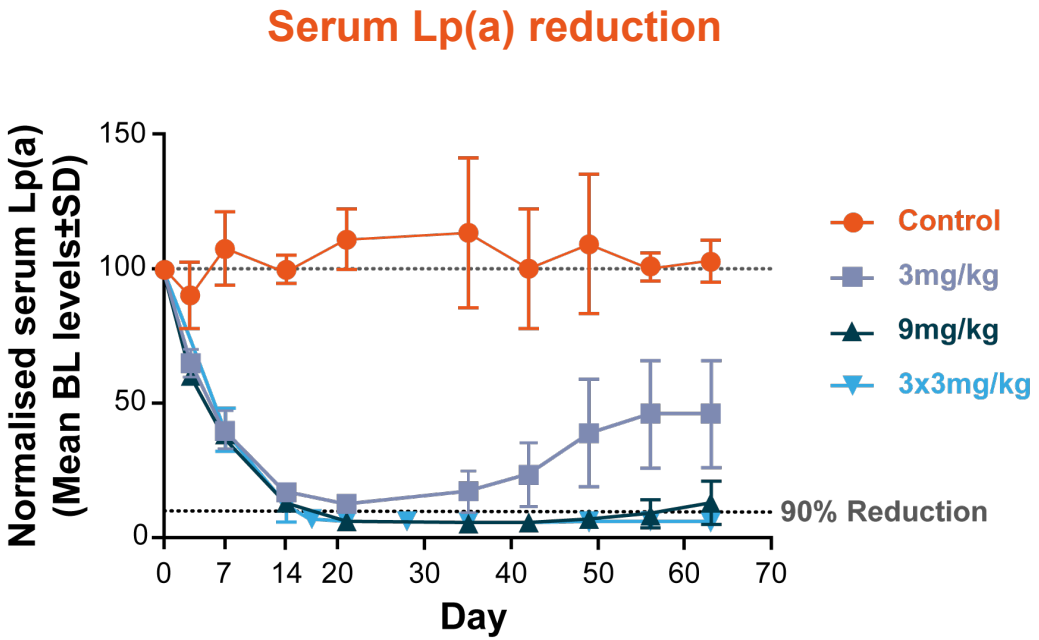
Blockbuster Potential

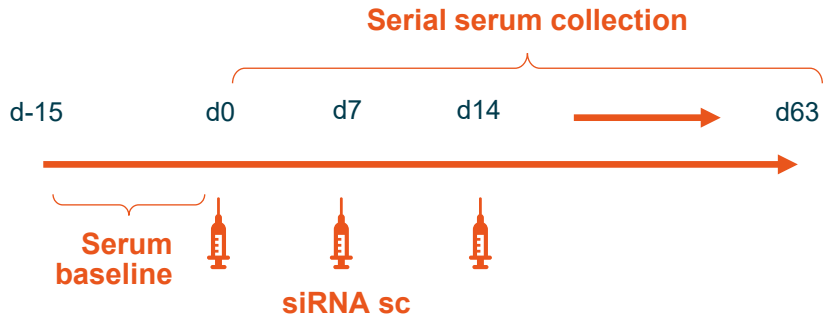
Sales of Cholesterol-Lowering Drugs Peaked at >$30B[3,4]

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) ≥ 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 atherosclerotic CVD 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

APOLLO

Reported positive data in SD study; MD study ongoing

PD = Pharmacodynamics; PK = Pharmacokinetics; CVD = Cardiovascular disease; MS = multiple dose; SD = single dose

Positive Topline Results from SLN360 Single-Ascending Dose Study in Healthy Adults with High Lp(a)

KEY TAKEAWAYS:

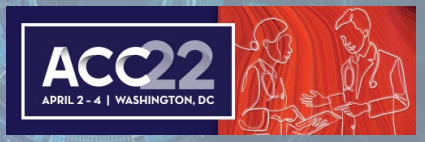
- SLN360 was well tolerated with no clinically important safety concerns identified
  - Low grade adverse events at the injection site were observed, most prominently at the highest dose
  - Systemic exposures (PK) of SLN360 increased in a broadly dose-proportional manner
- SLN360 reduced Lp(a) in a dose dependent manner from 46% up to a maximum of 98% with up to an 81% reduction persisting at 150 days
- Longer term follow up to 365 days ongoing

SLN360 Data Accepted for Late Breaking Presentation at The American College of Cardiology (ACC) Conference

SLN360 late-breaking presentation at the ACC 71st Annual Scientific Session:

"Magnitude And Duration Of Effects Of A Short-interfering RNA Targeting Lipoprotein(a): A Placebo-controlled Double-blind Dose-ranging Trial"

April 3, Washington D.C., United States





SLN124

Hepcidin Regulation Program

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

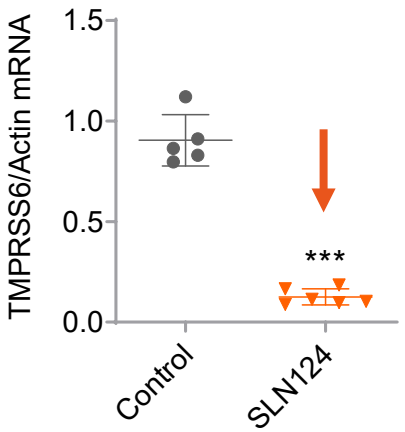
US rare pediatric disease designation for beta thalassemia

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

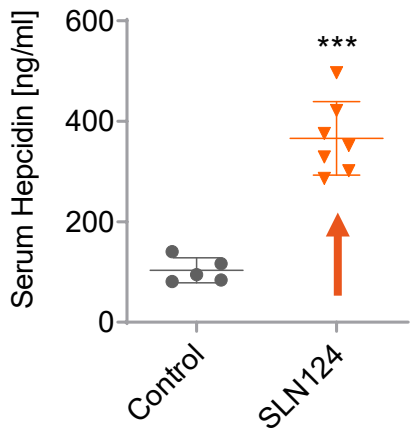
EU = European Union; MDS = myelodysplastic syndrome; US = United States

SLN124 is Designed to Restore Endogenous Hepcidin and Normalize Iron Levels

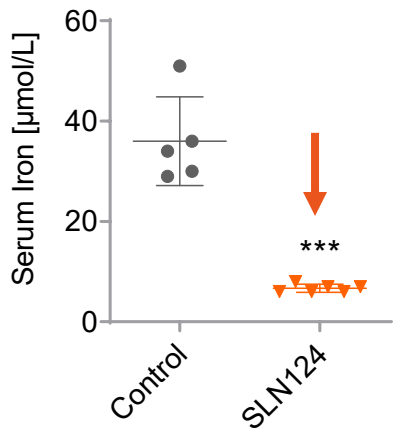
1 **Reduces TMPRSS6 in the liver**



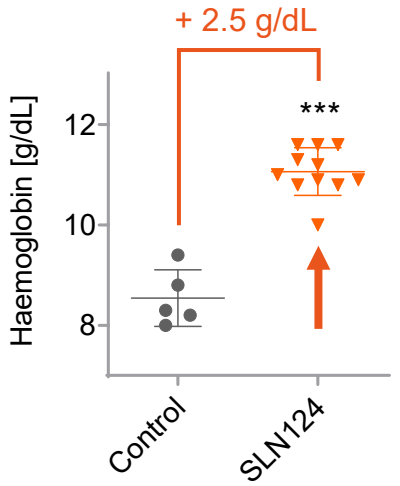
2 **Raises endogenous hepcidin**



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

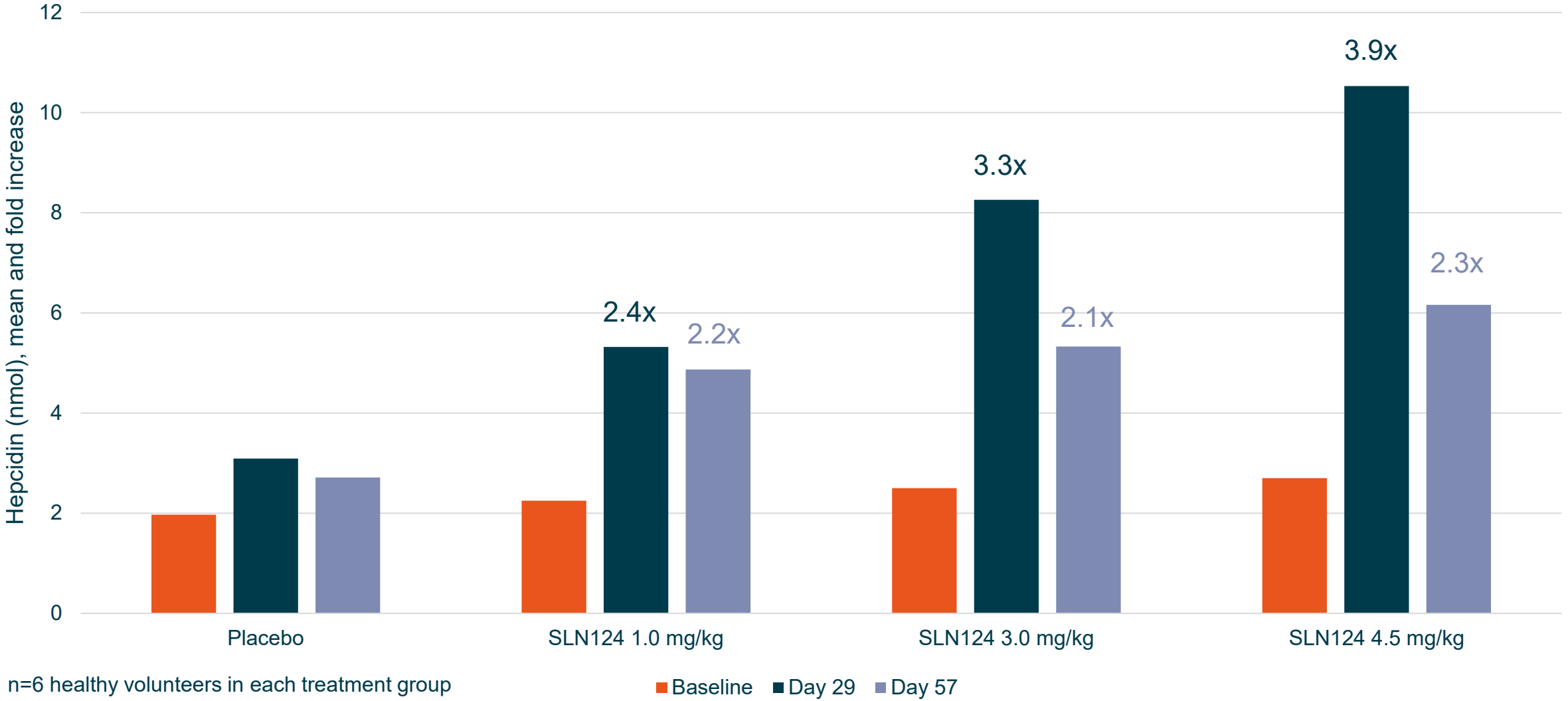
Design	Randomized, double-blind, placebo controlled, single dose study
Aim	Investigated the safety, tolerability, PK and PD response of SLN124 in healthy volunteers
Single Dose Cohorts	3 cohorts, 8 subjects per cohort (6 active, 2 placebo)
Dosing	1 mg/kg, 3 mg/kg and 4.5 mg/kg
Population	24 healthy adults

GEMINI

Data presented at ASH 2021

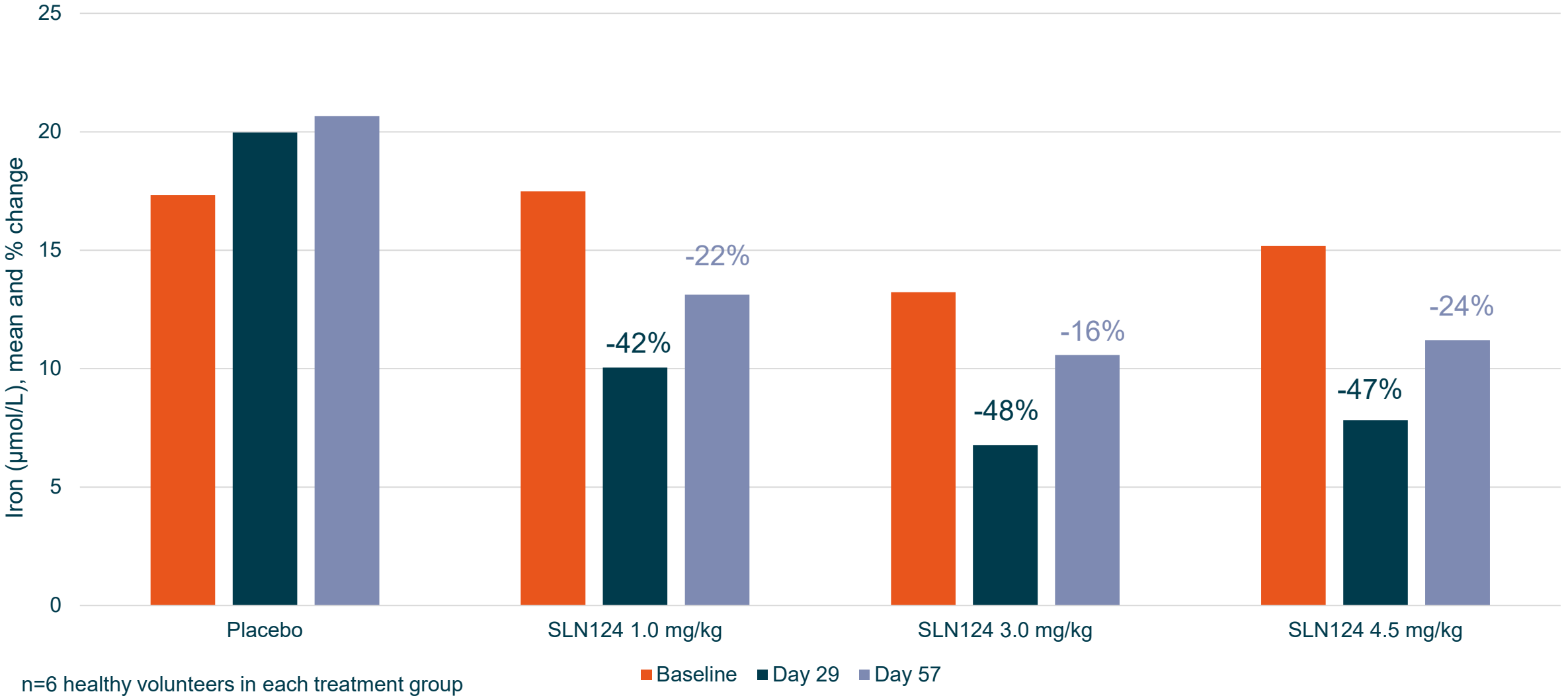
PD: Pharmacodynamics; PK: Pharmacokinetics

SLN124 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

Positive Results from SLN124 Healthy Volunteer Study

- First clinical data from **mRNAi GOLD™** platform
- Demonstrated proof of mechanism for SLN124
- All doses were well-tolerated with no serious or severe treatment emergent adverse events
- SLN124 increased average hepcidin up to ~4-fold and reduced serum iron by ~50% after a single dose with effects persisting for at least 2 months
- All SLN124 doses induced marked reductions in transferrin saturation (TSAT)
- Encouraging efficacy signal on serum iron and TSAT and favorable safety profile of SLN124 supports further development

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

GEMINI II

Single dose data expected in Q3 2022

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

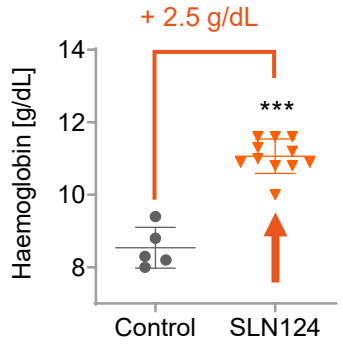
SLN124 Has The Potential For a Broad Mechanistic Mode-of-Action Approach

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**

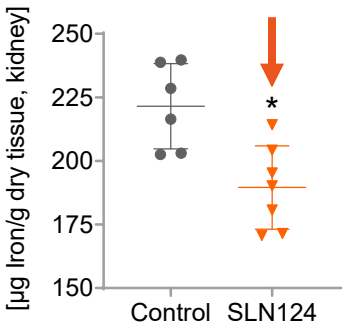
***Iron loading anemias** (e.g. beta thalassemia, MDS)* → **Reduce anemia**[1]

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



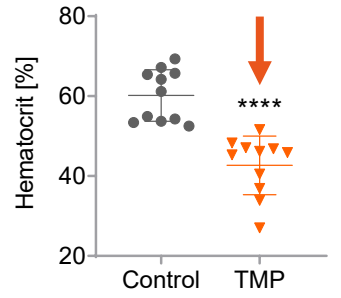
Hereditary hemochromatosis → **Prevent iron overload**[2]

Altamura et al., HemaSphere 2019 (PMID 31976476)



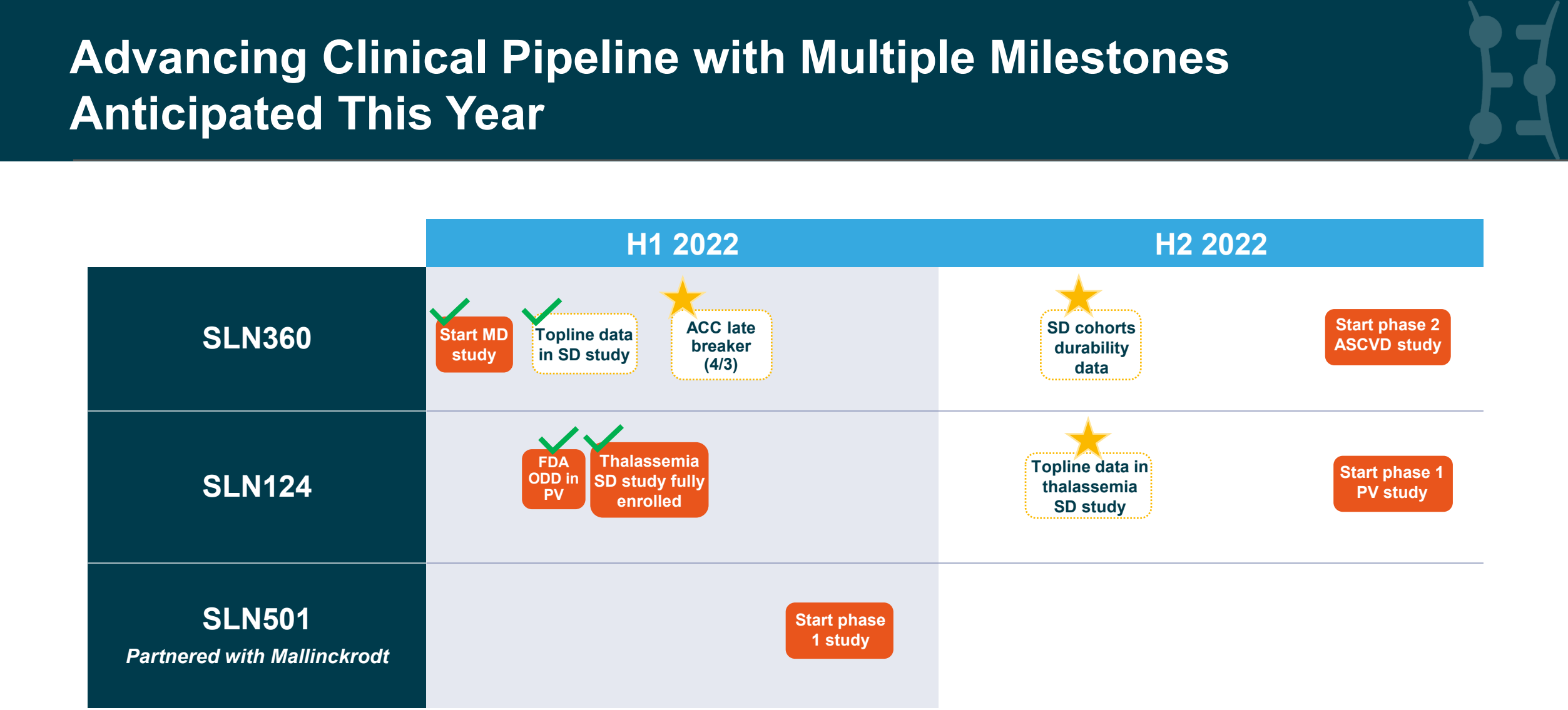
Polycythemia vera → **Reduce red packed cell volume**[3]

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

Advancing Clinical Pipeline with Multiple Milestones Anticipated This Year



ASCVD = atherosclerotic cardiovascular disease; SD = Single-ascending dose; MD = Multiple-ascending dose; PV = Polycythemia Vera; ODD = Orphan Drug Designation

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 (3/15/22)	$16.59 per ADS
Common Shares Outstanding (12/31/21)	89,784,720 / ~29,928,240 ADS
Market Capitalization (3/15/22)	~$497m / ~£381m
Cash (12/31/21)	~$99m / £73.5m
Debt	$0

Notes: ADS each represent 3 ordinary shares nominal value