SILENCE THERAPEUTICS

Silence Therapeutics

FY 2021 Results Call

March 2022

Forward-Looking Statements

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2021 Key Accomplishments

Reported first clinical data from **mRNAi GOLD™** platform

Established **clinical proof of mechanism** for SLN124 hepcidin regulation program

Completed **enrollment in SLN360 phase 1 study** in healthy volunteers with high lipoprotein(a)

Started **dosing patients in SLN124 phase 1** program

Secured new collaboration with **Hansoh Pharma**

Advanced **AstraZeneca** and **Mallinckrodt** collaborations

Maintained **strong financial** position

- $58m in non-dilutive cash from collaborations (AstraZeneca, Hansoh and Mallinckrodt)
- $45m private placement led by top US investors
- Completed AIM delisting and now trading exclusively on Nasdaq

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

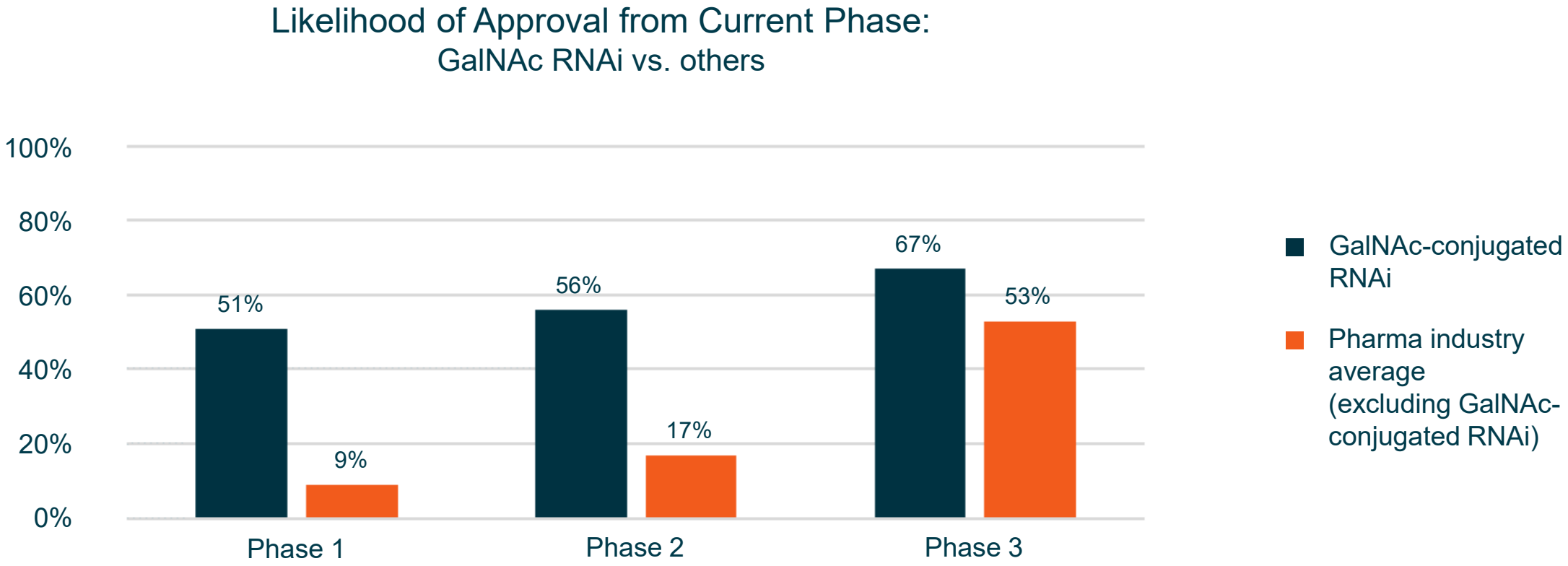
Engaged in global partnership discussions to maximize SLN360 program

- 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

Early-stage GalNAc-conjugated RNAi Programs Have a Much Greater Likelihood of Approval vs. Industry Average

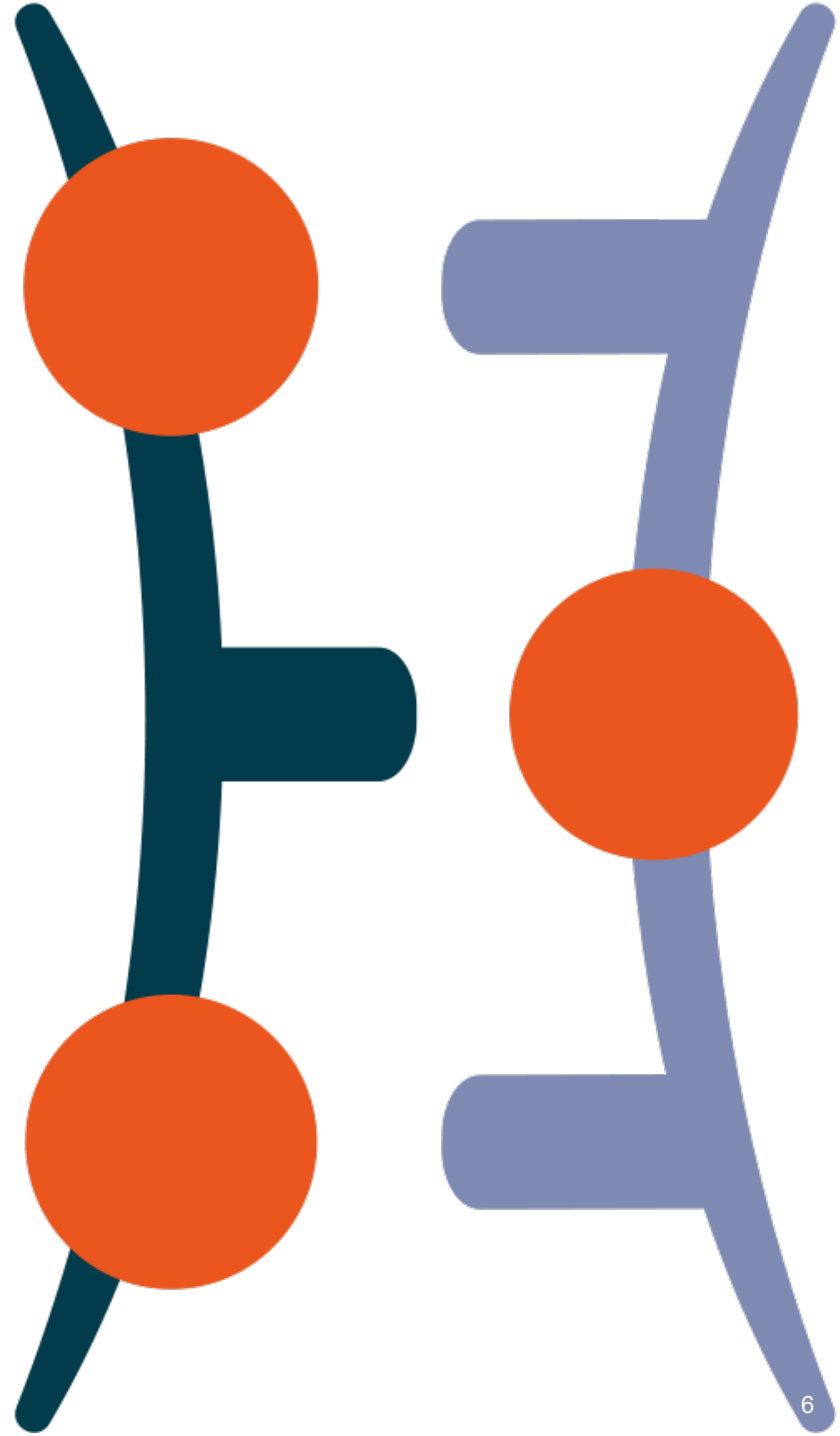


Phase success is defined as the movement of the program to the next phase, not an evaluation of whether endpoints were met.
GalNAc-conjugated RNAi includes both GalNAc-conjugated siRNA and GalNAc-conjugated ASO

Source: Pharmapremia, Informa Pharma Custom Intelligence analysis

FY21 Financials

Rhonda Hellums
CFO



Results of Operations

Consolidated Income Statement (GBP '000)	FY 2021	FY 2020
Revenue	£12.4m	£5.5m
Cost of sales	£7.5m	£3.8m
Research and development costs	(£30.8m)	(£20.2m)
Administrative expenses	(£20.0m)	(£14.0m)
Operating loss	(£45.8m)	(£35.8m)
Tax	£6.4m	£3.5m
Loss for the year after taxation	(£39.4m)	(£32.5m)

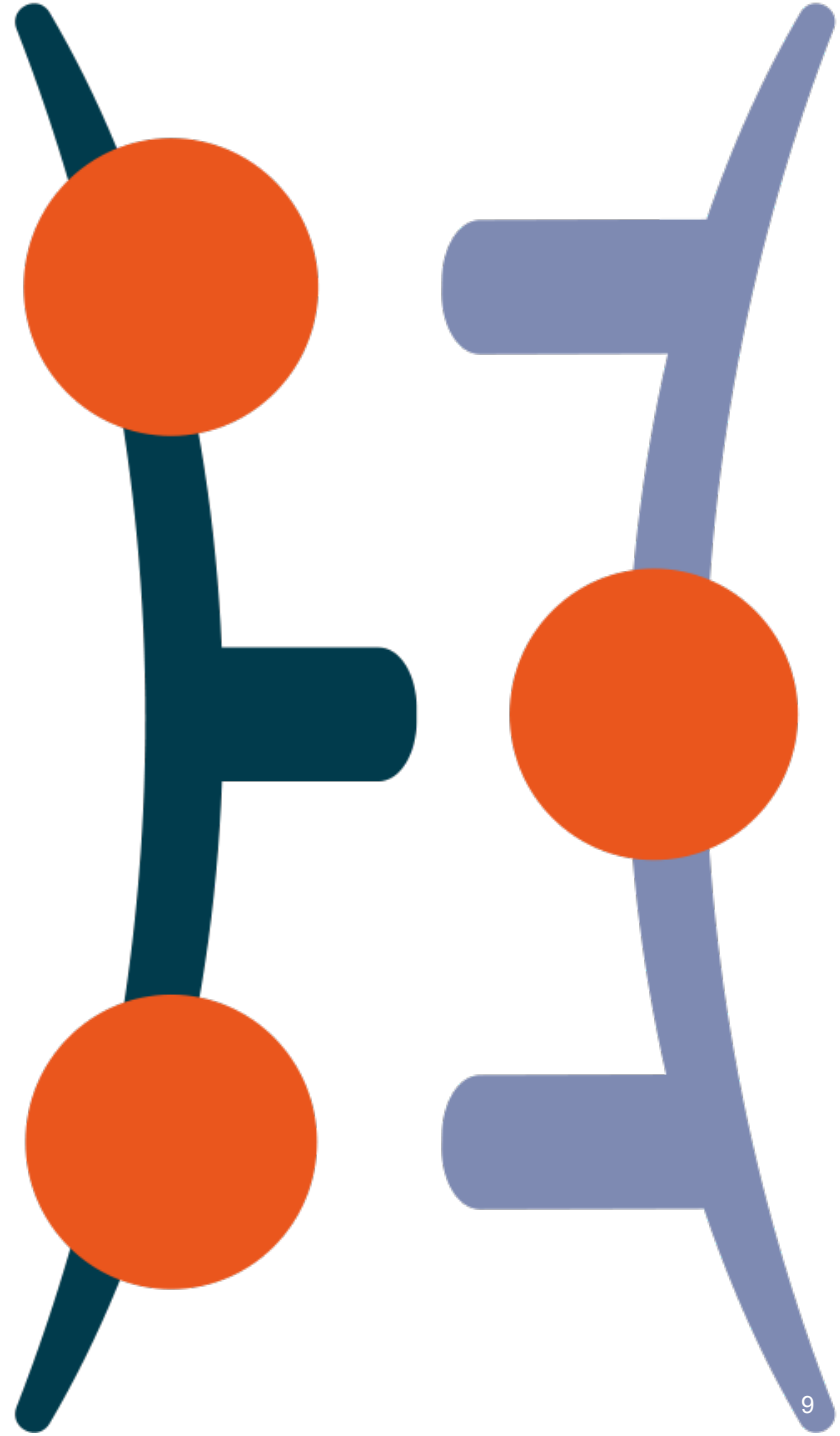
Financial Highlights

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

R&D Update

Giles Campion, MD
Head of R&D and CMO



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 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

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 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

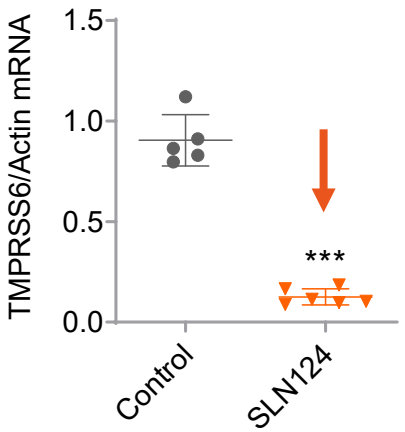
US rare pediatric disease designation for beta thalassemia

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

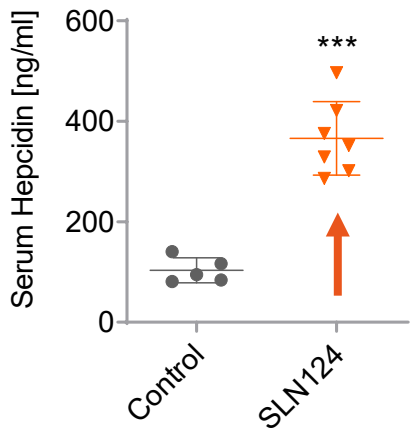
EU = European Union; MDS = myelodysplastic syndrome; US = United States

SLN124 is Designed to Restore Endogenous Hepcidin and Normalize Iron Levels

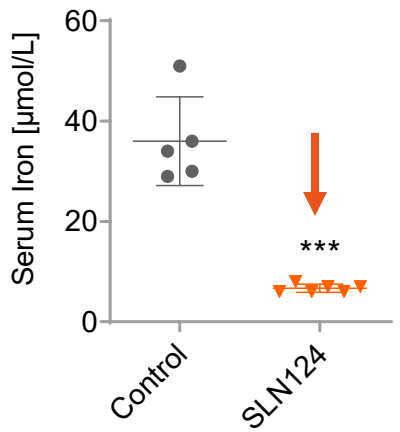
1 **Reduces TMPRSS6 in the liver**



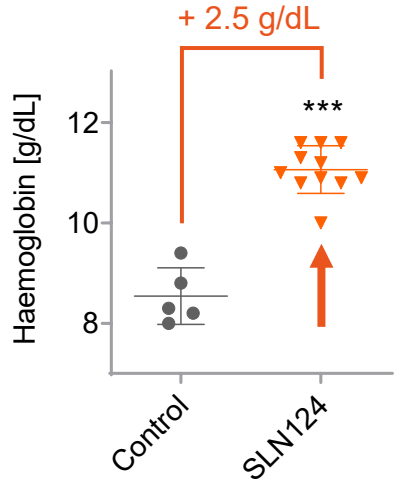
2 **Raises endogenous hepcidin**



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

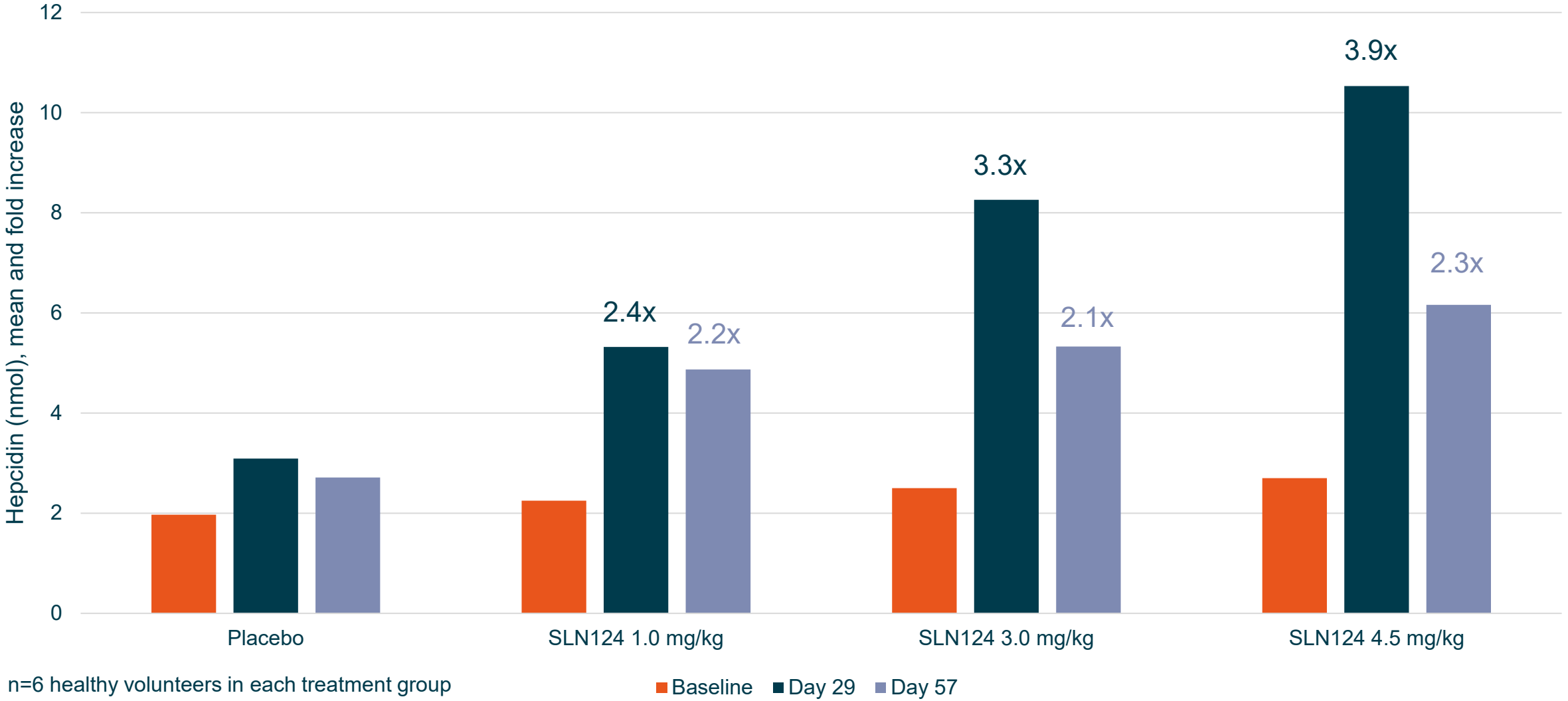
Design	Randomized, double-blind, placebo controlled, single dose study
Aim	Investigated the safety, tolerability, PK and PD response of SLN124 in 24 healthy volunteers
Single Dose Cohorts	3 cohorts, 8 subjects per cohort (6 active, 2 placebo)
Dosing	1 mg/kg, 3 mg/kg and 4.5 mg/kg

GEMINI

Data presented at ASH 2021

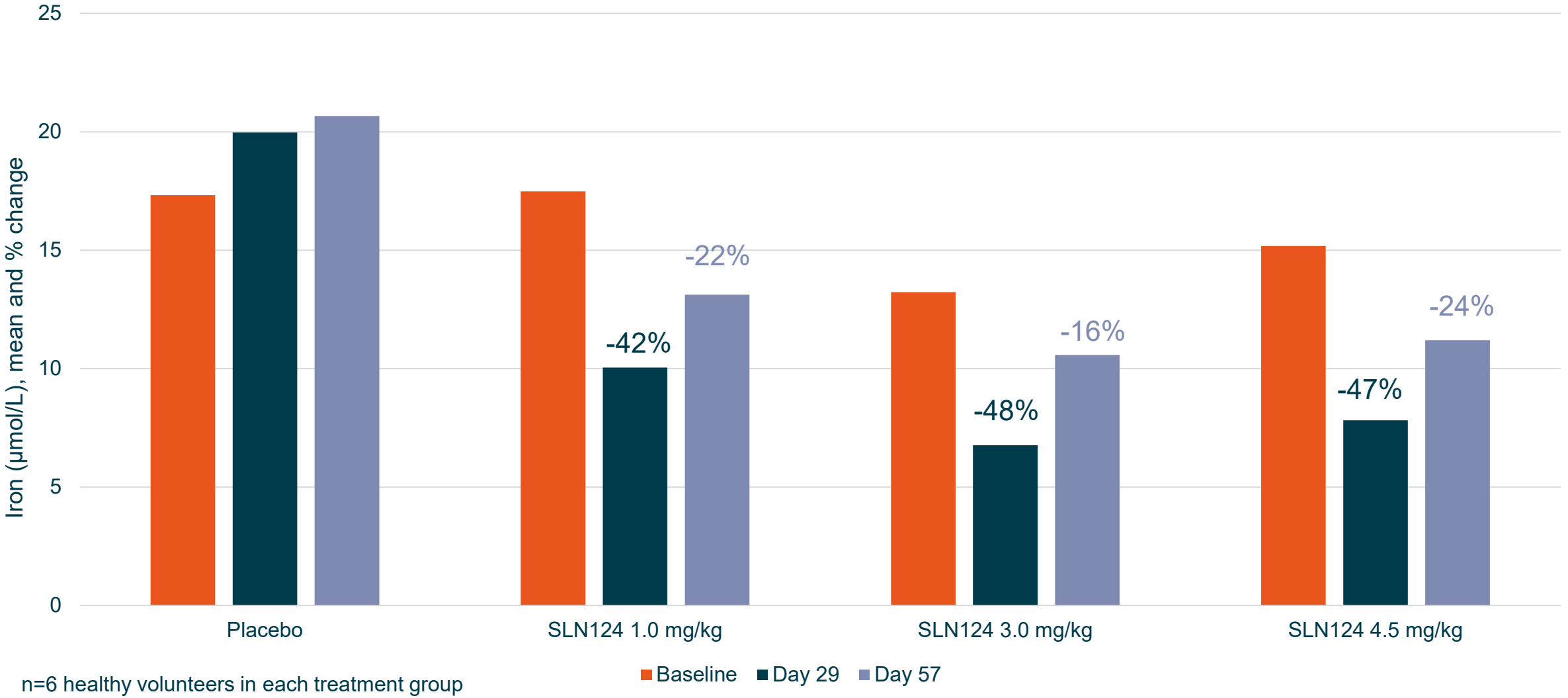
PD: Pharmacodynamics; PK: Pharmacokinetics

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

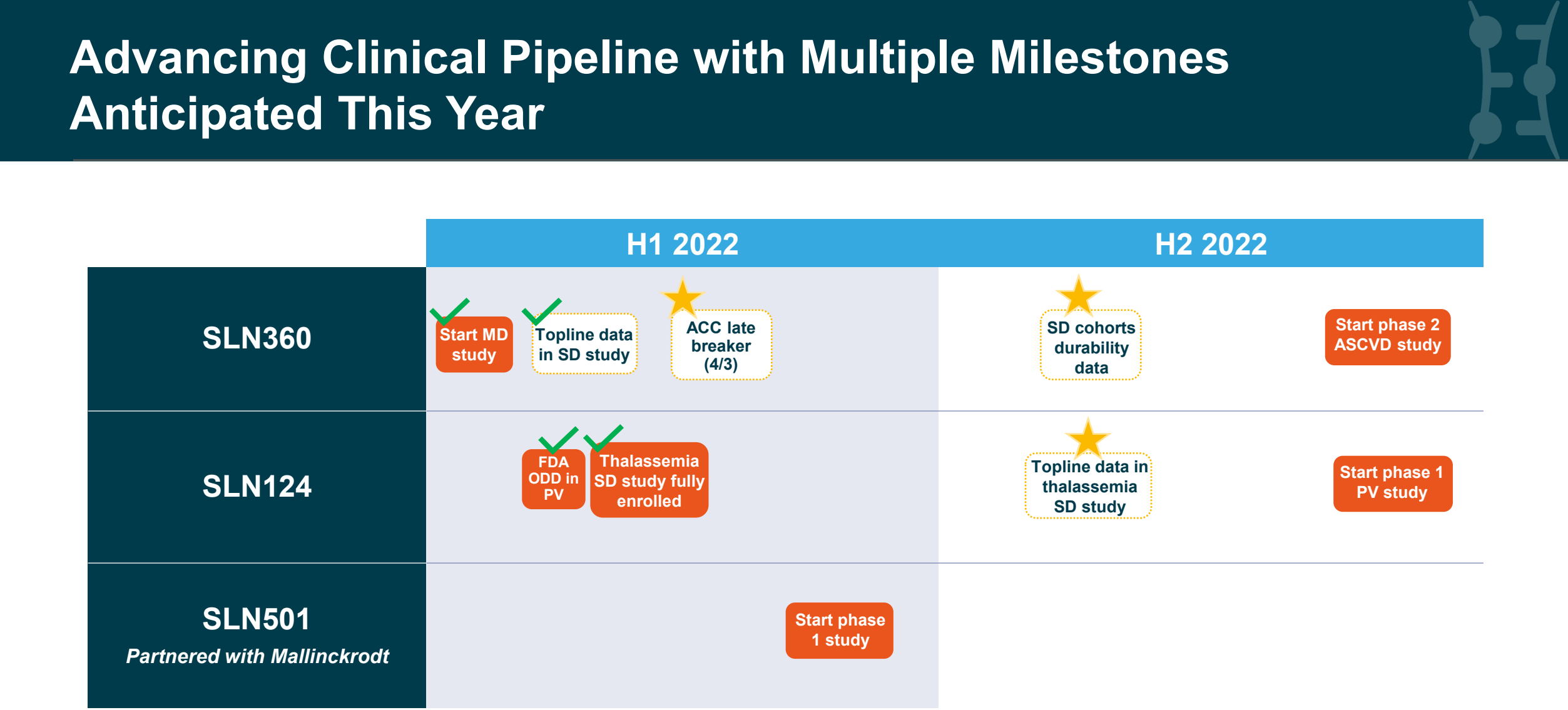
Design	Global, randomized, single-blind, placebo controlled single and multiple dose study
Aim	Investigate the safety, tolerability, PK and PD response of SLN124 in up to 56 adults with NTD thalassemia
Single Dose Cohorts	8 subjects per cohort, up to 4 cohorts
Multiple Dose Cohorts	8 subjects per cohort,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

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

Q&A

