SILENCE THERAPEUTICS

# Silence Therapeutics

## *Corporate Presentation*

November 16, 2020

# Forward Looking Statements

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# Key Investment Highlights

| | |
|---|---|
| **Pioneers in siRNA** | > siRNA designed to silence defective genes making disease causing proteins<br>> Pioneers in siRNA for over 18 years combined with broad IP estate are formidable competitive strengths |
| **Flexible GalNAc siRNA platform** | > GalNAc siRNA targets genetic diseases expressed in liver cells<br>> >7,000 proteins expressed in the liver |
| **Broad Pipeline** | > Mix of wholly owned clinical programmes and partnered programmes<br>> Advancing two wholly owned clinical programmes with expected data readouts next year<br>• SLN360 targeting high and prevalent unmet need in cardiovascular disease<br>• SLN124 targeting high unmet need in iron overload disorders |
| **Strong Financial Position** | > Cash runway extending beyond key data milestones for both SLN360 and SLN124 clinical programmes |
| **AIM and Nasdaq listed** | > Market cap ~£365m* with sites in London, New York and Berlin |

HQ in London

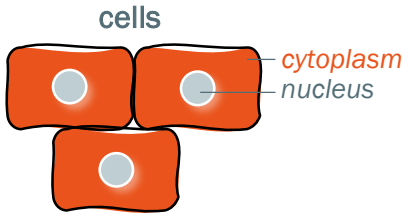
R&D in Berlin

+ New office in New York

Approx. 70 employees across all sites

*As of 6th November 2020

# siRNA Can Inhibit Expression of Disease-Associated Genes




## HEALTHY

DNA

Genes encode messages for all features in the body

nucleus

cytoplasm

mRNA

The information in DNA is transcribed into messenger RNA (mRNA) so it can be moved from the nucleus

Protein

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

## DISEASE

DNA

In certain diseases the DNA is mutated or abnormally expressed

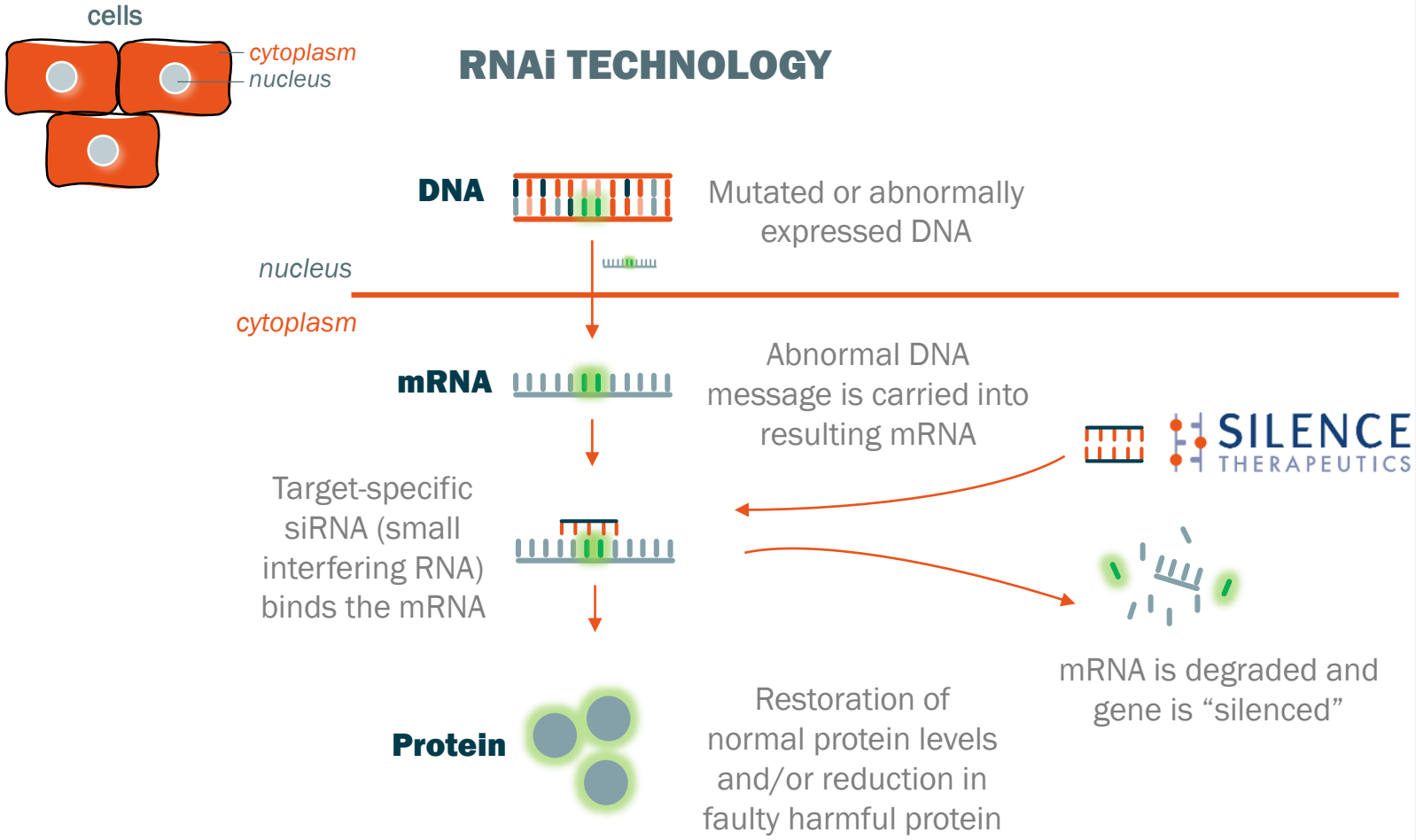
mRNA

Abnormal DNA message is carried into resulting mRNA

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




## Natural

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

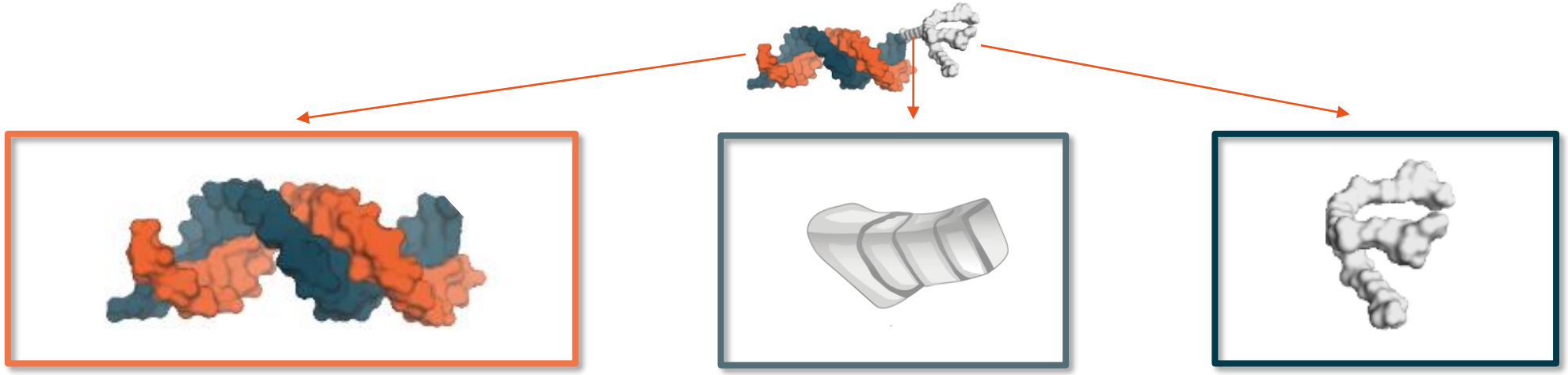
## Durable

Long-lasting gene knockdown possible for > 2 months following a single injection

## Safe

siRNA specifically designed to bind only to target sequence

# siRNA is linked to a GalNAc Ligand to target liver cells



## siRNA molecule

> Unique stretch of RNA matched to target gene

> Silence has developed unique chemical modifications that enhance stability and improve activity

> Unlike antisense oligonucleotides, siRNA molecules are double stranded resulting in improved safety

## Linker

> Silence has developed proprietary linkers, enabling the attachment of targeting ligands to the siRNA molecule

## Ligand

(targeting moiety)

> The ligand is responsible for the delivery of the molecule to specific tissues/cells

> Silence uses a GalNAc ligand to target liver cells

**Continuous Fine-Tuning to Further Improve Performance**

siRNA: small interfering RNA

# 3 Pillars to our Business

- ✓ **Deliver Partnership Programmes**
- ✓ **Advance Proprietary Pipeline**
- ✓ **Enable Delivery of siRNA Outside the Liver**

# Partnership Programmes Further Expand Pipeline and Provide Up to $6 Billion in Potential Milestones Plus Royalties

AstraZeneca

- Signed major deal to discover, develop and commercialise 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
  - Up to $2 billion in potential milestones plus royalties for 3 targets
  - Exercised option to license 3 complement targets

Takeda

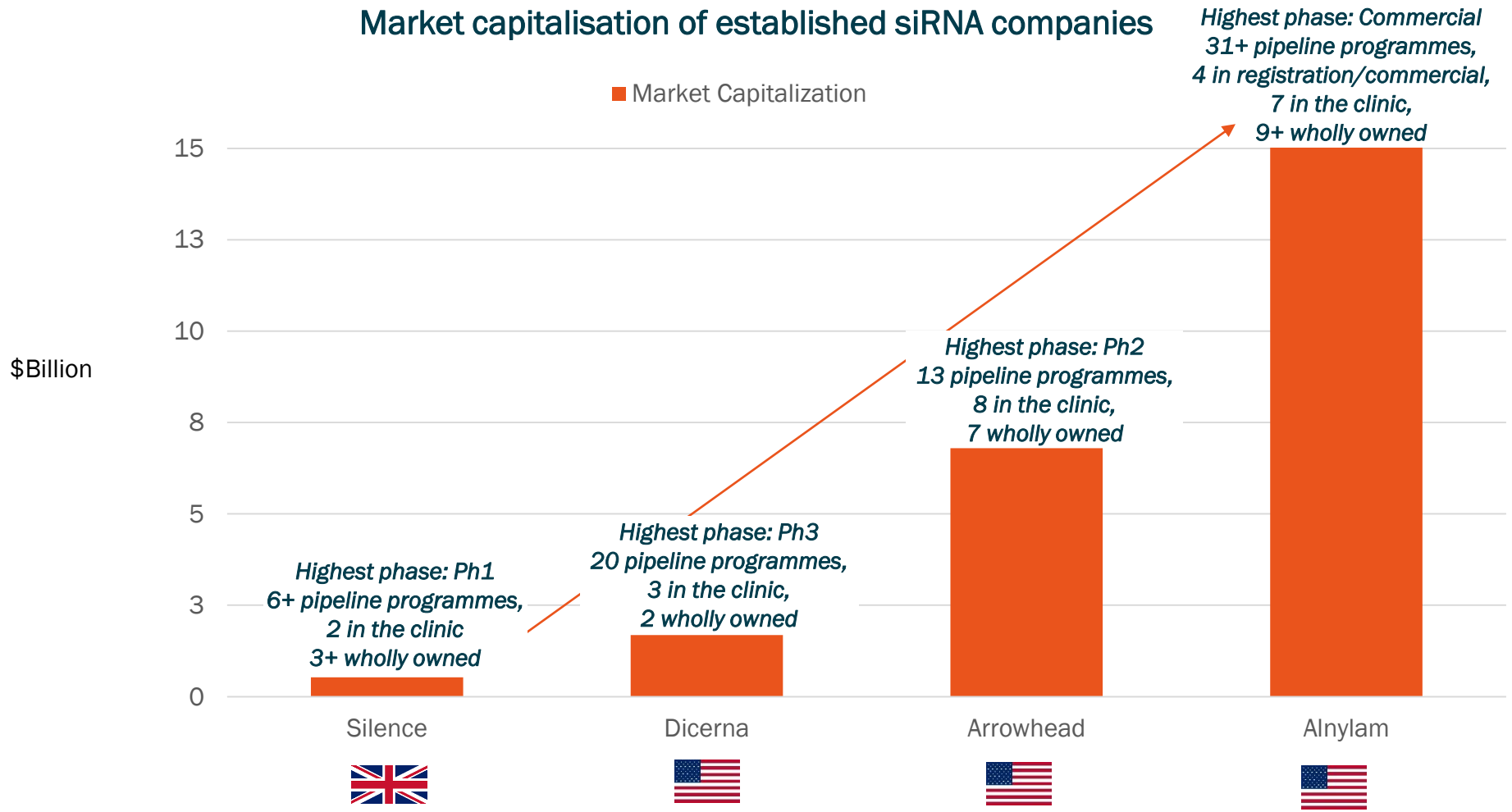
- Commenced technology evaluation to explore the potential of using our platform to generate siRNA molecules against a novel, undisclosed target in January 2020

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

# Mix of Proprietary Pipeline Programmes and Partnered Programmes – Multiple Shots on Goal

| Programme | Indication | Target | Discovery | Preclinical | Phase I | Phase II | Phase III | Proprietary/Partnered |
|---|---|---|---|---|---|---|---|---|
| SLN360 | Cardiovascular disease with high Lp(a) | Lp(a) | | | | | | SILENCE THERAPEUTICS |
| SLN124 | ß-Thalassaemia<br>Myelodysplastic Syndrome | TMPRSS6 | | | | | | SILENCE THERAPEUTICS |
| SLN500 | Complement-mediated diseases | C3 | | | | | | Mallinckrodt<br>Options exercised on 3 complement targets |
| SLN-MNK-2 | | 2nd complement target | | | | | | |
| SLN-AZ-1 | Undisclosed | Undisclosed | | | | | | AstraZeneca<br>5 CVRM/respiratory targets w/in 3 years |
| Multiple programs | Undisclosed | Undisclosed | | | | | | SILENCE THERAPEUTICS |

# SLN Recent Nasdaq Listing Opens Door to New Investors and Provides Significant Growth Opportunity




Notes:

Market Capitalization as of November 6, 2020

Pipeline programmes = company disclosed partnered and wholly owned programmes discovery phase – marketed

# SLN360 Targets Lp(a) - an Independent Risk Factor for Cardiovascular Disease

Lp(a) levels are genetically determined

Recognised as a major untreated risk factor in cardiovascular disease

Lp(a) levels are not significantly modifiable through diet or approved pharmacological therapies

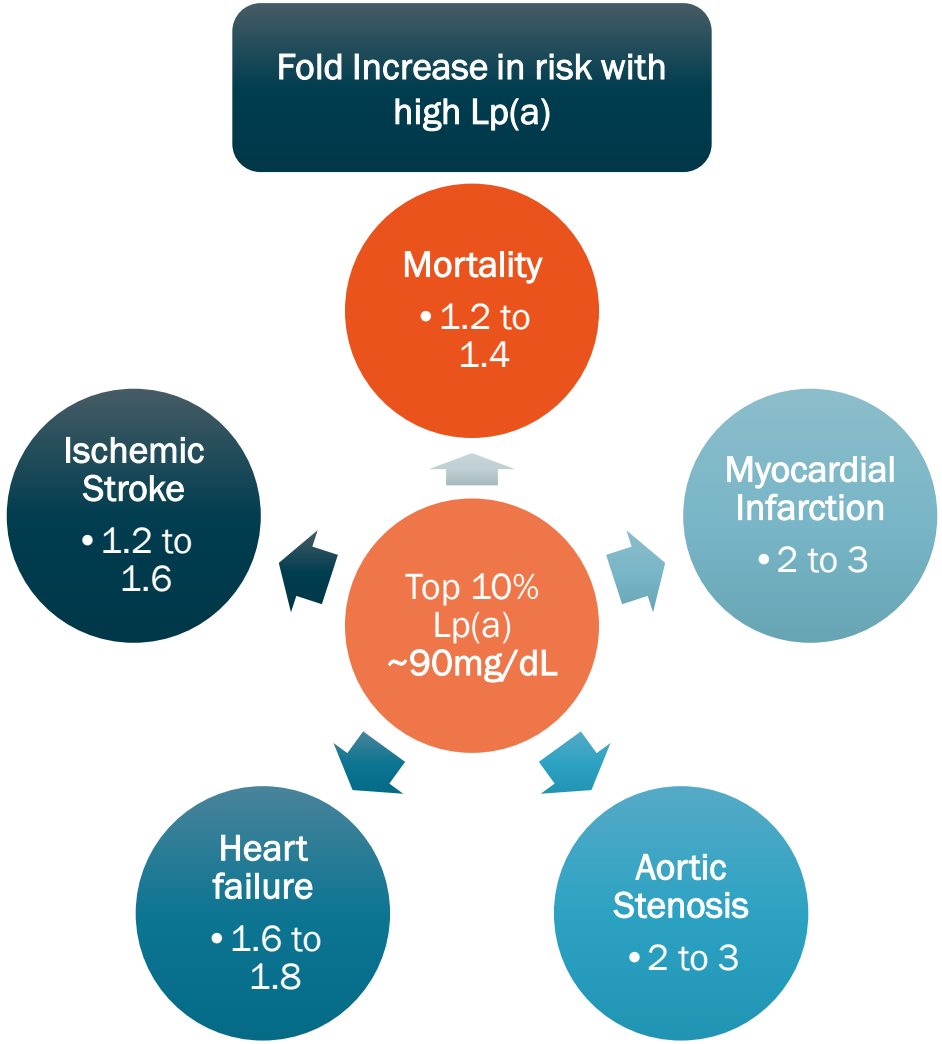
Large population worldwide with up to 10% with >90mg/dL (2x increased MI risk)

*Targeting Lp(a) with SLN360 has the potential to address major unmet needs in cardiovascular disease*

# Cardiovascular Event Risk Increases with High Lp(a)

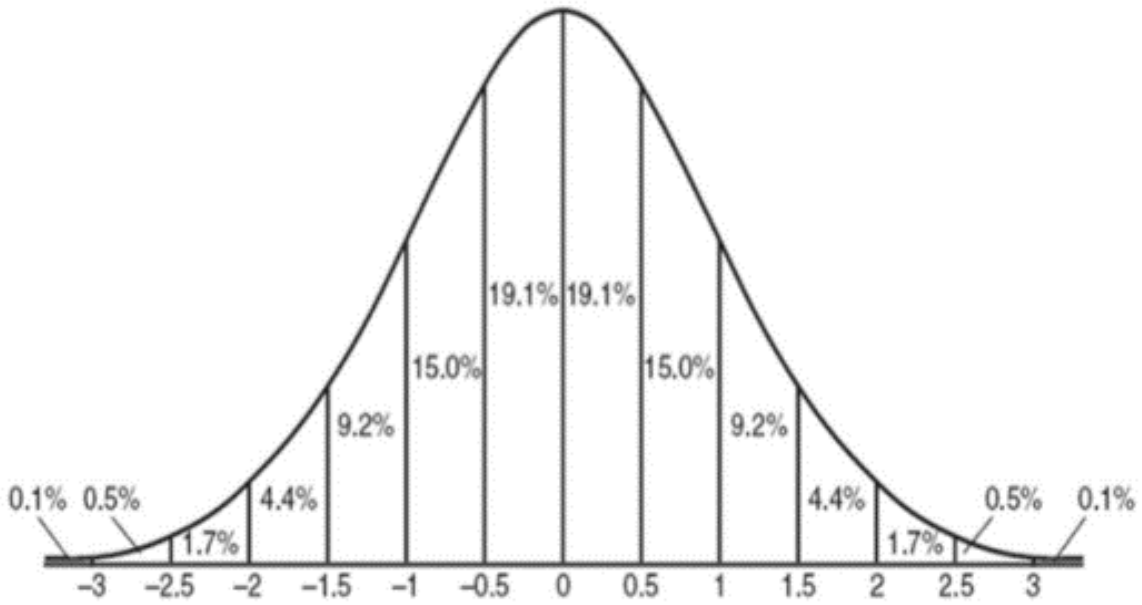
**Risk Ratio:**

- The probability of one outcome versus another.
- A risk ratio of 2 is double the risk.
- A risk of 0.5 is half the risk

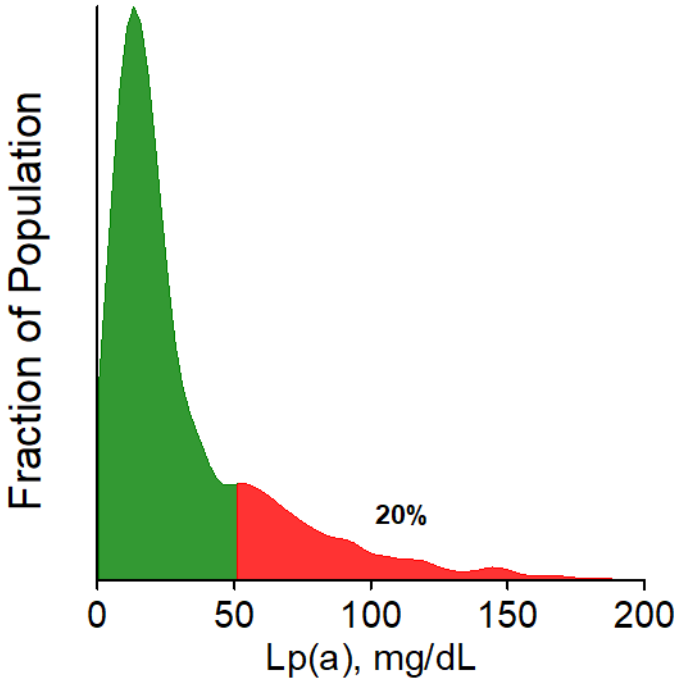


# Lp(a) Distribution in the Population

Most biological entities show a normal distribution in a population

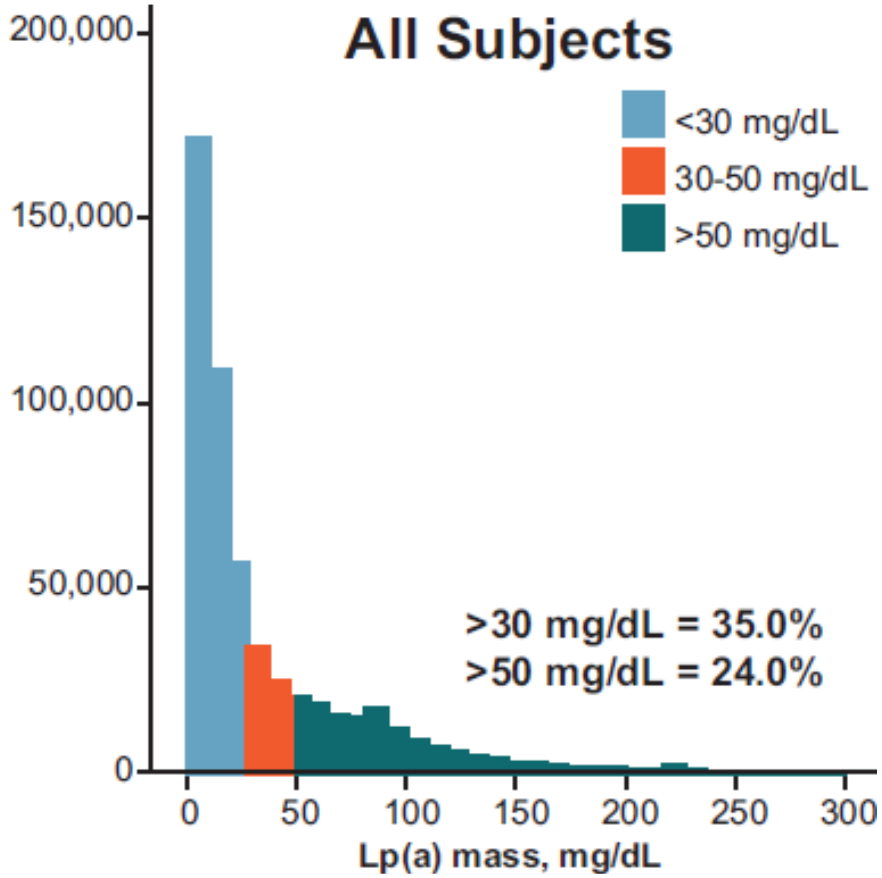



Lp(a) distribution is skewed with 20% of the population with higher than 50 mg/dL




*Nordestgaard B Eur Heart J:* 2010 31:2844

# Up to 700 Million Globally in Top 10% Lp(a) Levels




Source: US laboratory Database in 531,144 patients

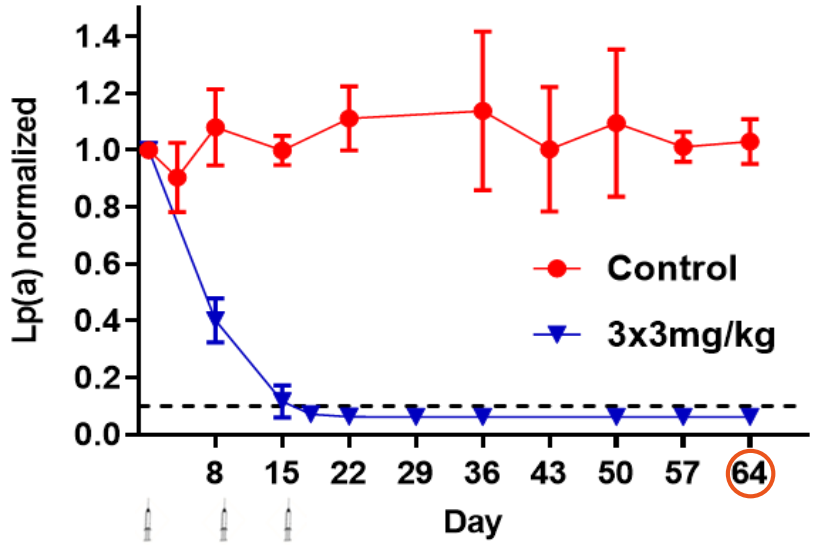
## Global Prevalence of Elevated Lp(a) [millions]

| Prevalence | 20% | 10% | 5% | 1% |
|---|---|---|---|---|
| *Lp(a) [mg/dL]* | *60* | *90* | *116* | *180* |
| USA | 64 | 30 | 16 | 3.2 |
| EU | 150 | 75 | 37.5 | 7.5 |
| Globally | 1400 | 700 | 350 | 70 |

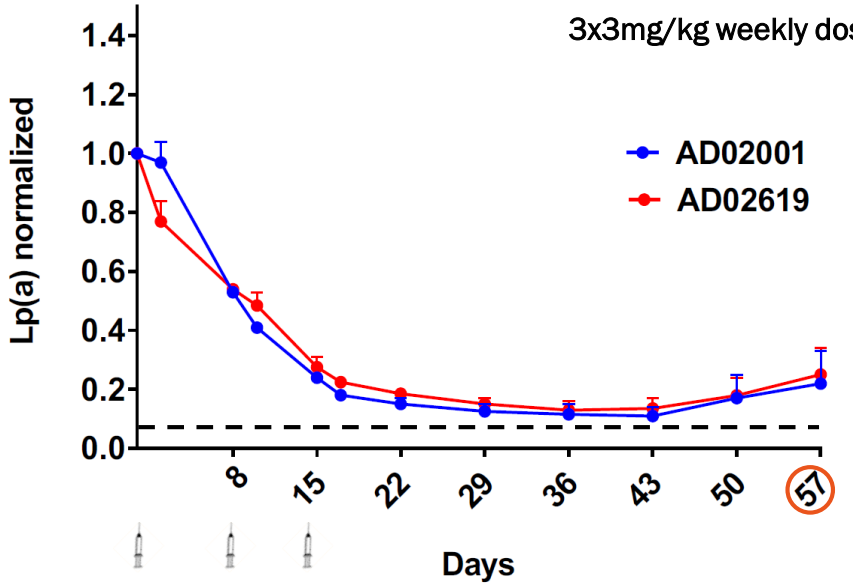
Varvel et al Arterioscler Thromb Vasc Biol. 2016;36:2239

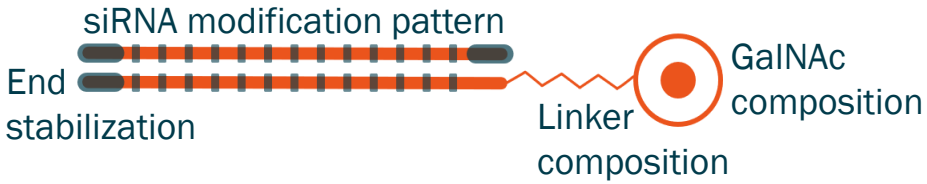
# SLN360 Demonstrated Highly Competitive Preclinical Profile – More Robust Knockdown and Longer Lasting

## SLN360 (wholly owned by Silence)




## AMG 890 (Amgen / Arrowhead)




AMG 890 chart reproduced from Melquist et al "Targeting apolipoprotein(a) with a novel RNAi delivery platform as a prophylactic treatment to reduce risk of cardiovascular events in individuals with elevated lipoprotein(a)" AHA 2016 Scientific Sessions

# 3 Phase 1 Study Readouts Anticipated in 2021

| Programme | 2H 2020 | | 1H 2021 | 2H 2021 |
|---|---|---|---|---|
| SLN360 for cardiovascular disease with high Lp(a) | | Initiate dosing in Phase I trial healthy volunteers and secondary prevention patients with elevated Lp(a) | | ★ Data from Phase I trial healthy volunteers and secondary prevention patients with elevated Lp(a) |
| SLN124 for iron overload disorders | ✓ Initiate dosing in healthy volunteer study | Initiate dosing in Phase 1 patient study | ★ Data from healthy volunteer study | ★ Data from Phase 1 patient study |

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

★ = data milestone

# Financial Highlights

| SLN – AIM and Nasdaq listed | |
|---|---|
| Stock Price (11/06/20) | 437p / $15.76 |
| Common Shares Outstanding (6/30/20) | ~82.83m |
| Market Capitalization (11/06/20) | ~£365m /~$480m |
| Proforma cash balance (6/30/20)* | $102m |
| Debt | 0 |

*Pro-forma cash balance is $102m (£50.3m converted at 1.23 (USD:GBP at 30 June) plus $40m due from AZ in H1 2021)

# Appendix

# SLN124
## for the treatment of

# Iron Overload Disorders

# SLN124 Market Opportunity

## US and EU patients

### β-Thalassemia

~40,000 TDT[1]
~20,000 NTDT[2]

**Onset:** from birth, but notable incidence of NTDT beyond 35

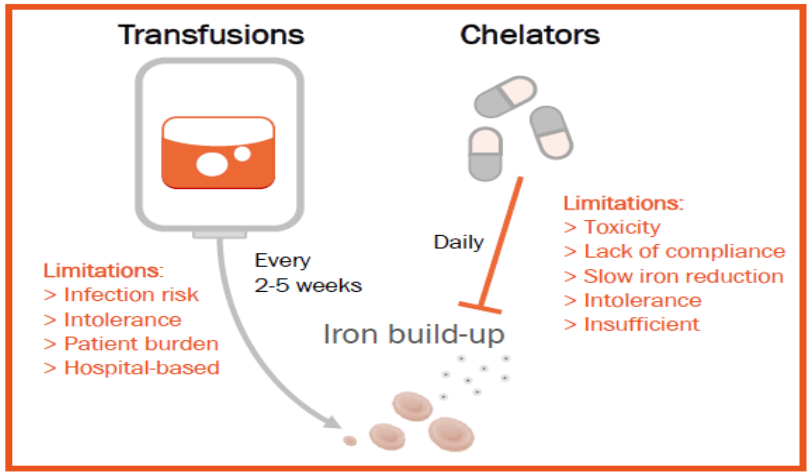
### MDS[3]

>100,000

**Onset:** Typically >70y

Orphan indications

## Standard of Care




## Benefits of SLN124

SLN124 aims to:

1. Reduce organ iron levels &
2. Enhance erythropoiesis

↓

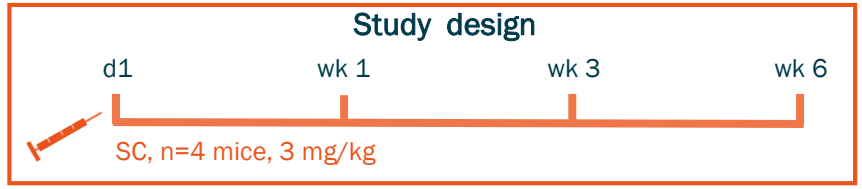
Reduced transfusion frequency &
Secondary iron overload burden

## Advantages v Competition

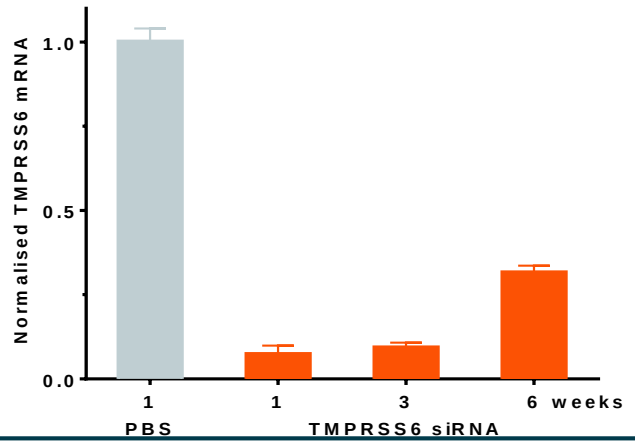
| Advantages | Competition |
|---|---|
| Quality of Life | **SoC:** Transfusions + Chelators |
| Safety | Antisense RNA |
| Organ iron levels | Luspatercept |
| Compliance | Gene therapy |
| Less frequent dosing | Hepcidin mimetics |

Notes: 1 TDT = Transfusion Dependent Thalassemia 2 NTDT = Non Transfusion Dependent Thalassemia 3 MDS = Myelodysplastic Syndrome

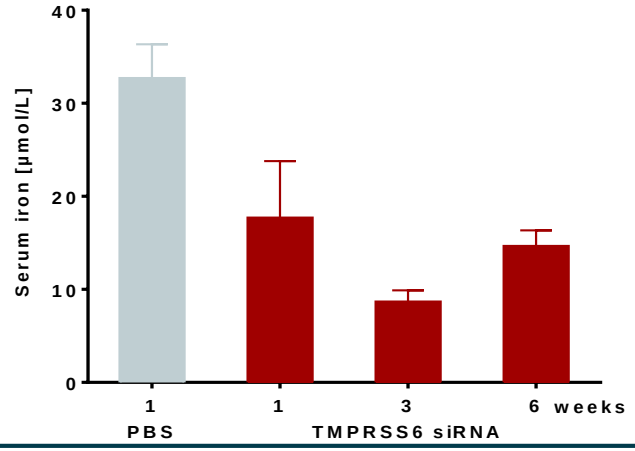
# SLN124 Lowered Iron levels for at Least 6 Weeks After Single Administration in Animal Model




## TMPRSS6 mRNA (liver)




## Iron (serum)



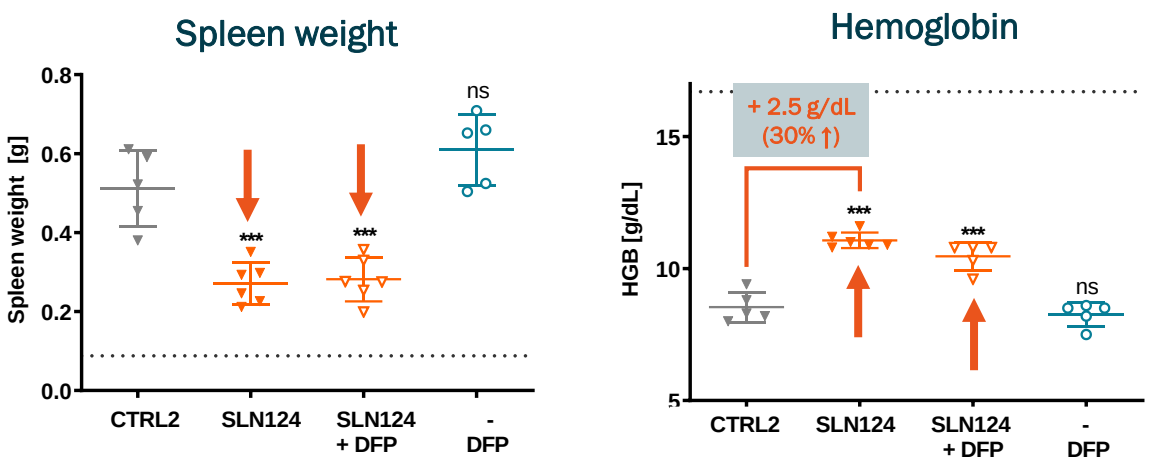

- Long-lasting functional mRNA KD in liver
- Reduction of serum iron levels for at least 6 weeks
- Well tolerated with long duration of action in mice

# SLN124 Lowered Spleen Weight, Increased Red Blood Cell Count and Reduced Need for Transfusions in Animal Model

**Study design**

$Hbb^{th3/+}$ mice, 2-4 m, n=5-8
2x 3mg/kg SLN124 s.c.
1.25 mg/ml deferiprone in drinking water


Collaboration with
Dr. J. Vadolas & Dr. G. Grigoriadis
Monash Medical Centre/Melbourne, Australia




- **Hb ↑ by ≥1.5 g/dL defined as "clinically relevant effect"**[1]
- No Δ Hb with 5-weeks DFP exposure
- ↓ need for blood transfusions by ↑ Hb (reflects 2-3 units of RBC)[2]

> SLN124 ameliorates splenomegaly; no impact by iron chelator DFP
> SLN124 improves anemia and ↓ the need for RBC transfusions
> No effect by DFP alone, SLN124 effect maintained in the presence of DFP

[1]Platzbecker et al., Blood 2019; [2]Bosch et al., Vox Sang 2017

# Leadership

## President and CEO
## Mark Rothera

- Appointed as President and CEO in September 2020
- Over 30 years of experience in the biopharmaceutical industry including driving the transition of multiple emerging biotech companies from R&D stage to commercialisation
- Former President & CEO of Orchard Therapeutics and CCO of PTC Therapeutics

## EVP, Head of R&D and CMO
## Giles Campion

- Former Chief Medical Officer and SVP R&D at Prosensa (2009-2016), playing a major role in their Nasdaq IPO and subsequent sale to Biomarin for $680m
- Most recently CMO at Albumedix
- Spent 4 years in senior R&D roles at Novartis
- Medical degree and doctorate from Bristol University

## CFO
## Rob Quinn

- Chartered accountancy training at Deloitte before joining GSK
- Area Finance Director for Africa and Developing Countries at GSK
- Joined Silence in early 2017 as Head FP&A
- PhD in Biochemistry from the University of Manchester

# Internal Know-How and Intellectual Property

- **Modification pattern**: number of non-natural modifications reduced from c.50% to <15% through the discovery of novel modification patterns
- **End stabilisation:** increased circulation half-life, increased activity and duration of action
- **Linker:** simplified and flexible synthesis, increased activity, and option to control circulation and intracellular half-life
- **GalNAc:** 2-3 fold increase in activity achieved through optimization of number and placement of GalNAc units
- **IP:** 10 siRNA chemistry patent applications filed 2017-2019