SILENCE THERAPEUTICS

Silence Therapeutics

Corporate Presentation

November 2020

Forward Looking Statements

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Key Investment Highlights

Pioneers in siRNA

> siRNA designed to silence defective genes making disease causing proteins

> 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

> >7,000 proteins expressed in the liver

Broad Pipeline

> Mix of wholly owned clinical programmes and partnered programmes

> Advancing two wholly owned clinical programmes with expected data readouts next year
- SLN360 targeting high and prevalent unmet need in cardiovascular disease
- 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

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Led by an International, Sector-Experienced Board and Executive Leadership Team

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



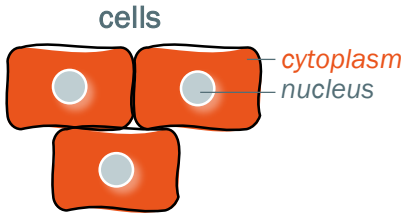
CFO
Rob Quinn

- 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



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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

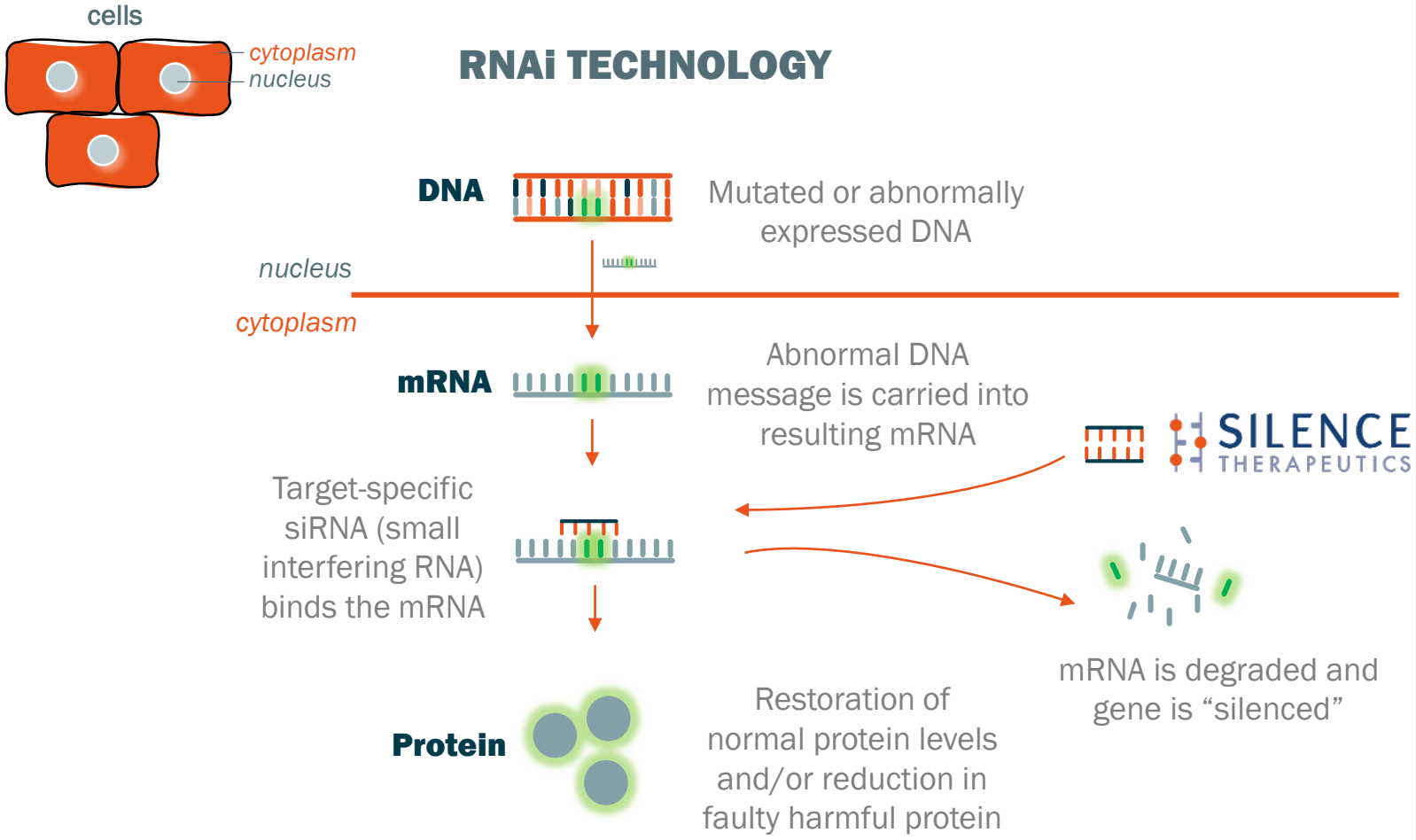
Protein

In some cases mutations instruct the cell to produce too much protein or the protein made does not work

siRNA: short interfering ribonucleic acid

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siRNA Can Precisely Target and Silence Disease-Associated Genes



Natural

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

Durable

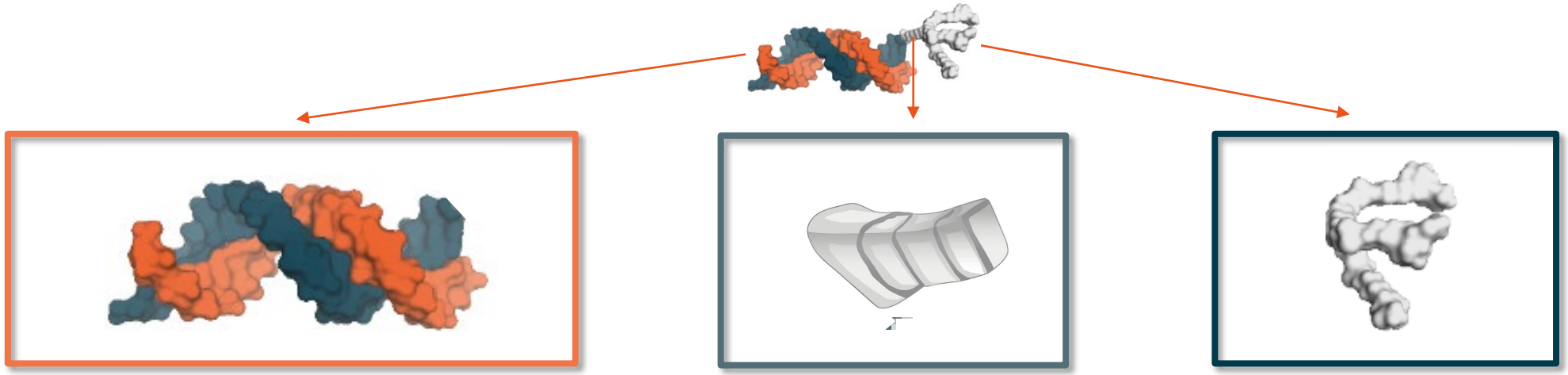
Long-lasting gene knockdown possible for > 2 months following a single injection

Safe

siRNA specifically designed to bind only to target sequence

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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

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3 Pillars to our Business

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

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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 commercialisation 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.

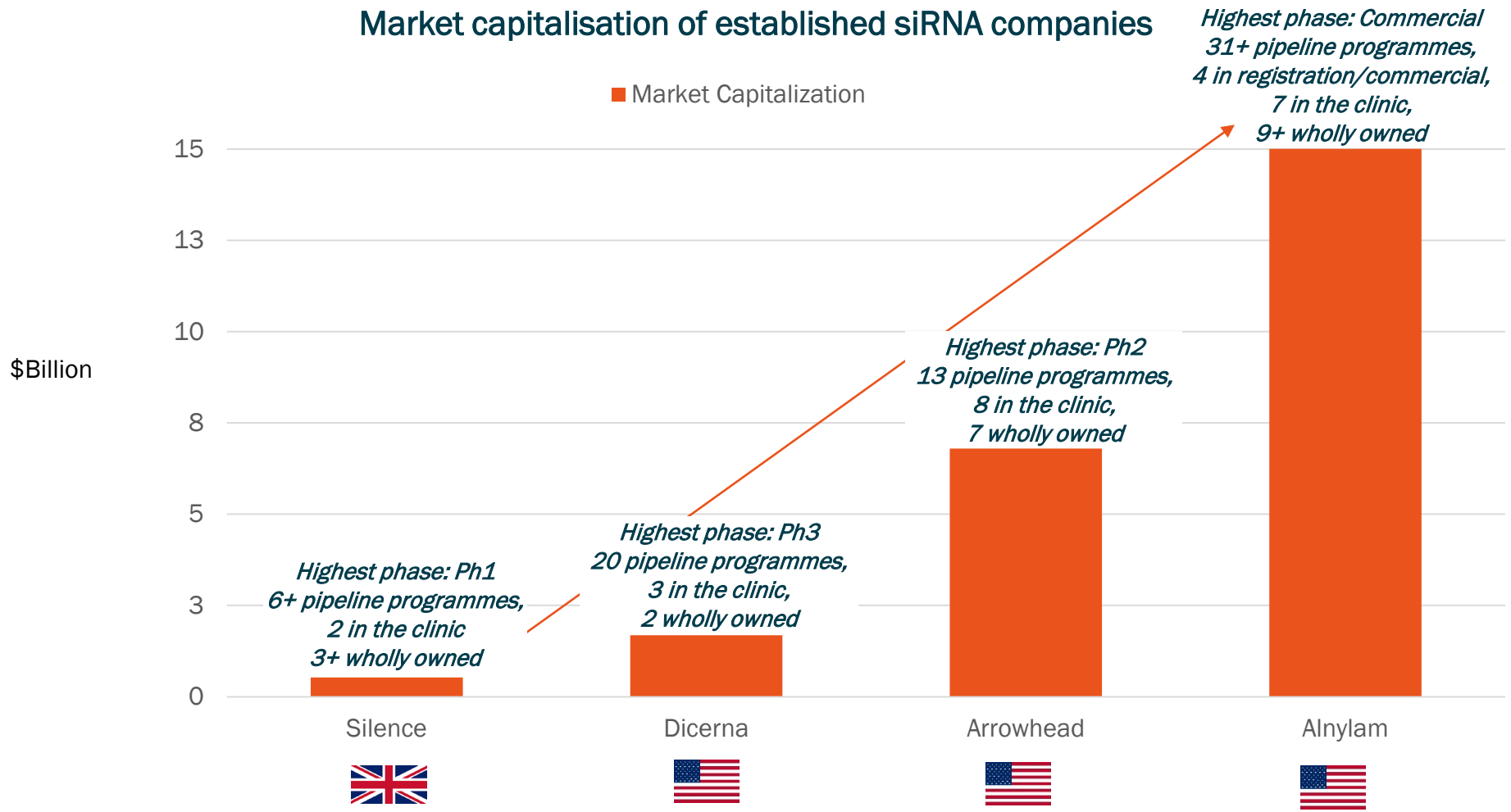
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Mix of Proprietary Pipeline Programmes and Partnered Programmes – Multiple Shots on Goal

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 Myelodysplastic Syndrome	TMPRSS6						SILENCE THERAPEUTICS
SLN500	Complement-mediated diseases	C3						Mallinckrodt Options exercised on 3 complement targets
SLN-MNK-2		2nd complement target						
SLN-AZ-1	Undisclosed	Undisclosed						AstraZeneca 5 CVRM/respiratory targets w/in 3 years
Multiple programs	Undisclosed	Undisclosed						SILENCE THERAPEUTICS

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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

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SLN360
for the treatment of

Cardiovascular Disease with high Lp(a)

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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

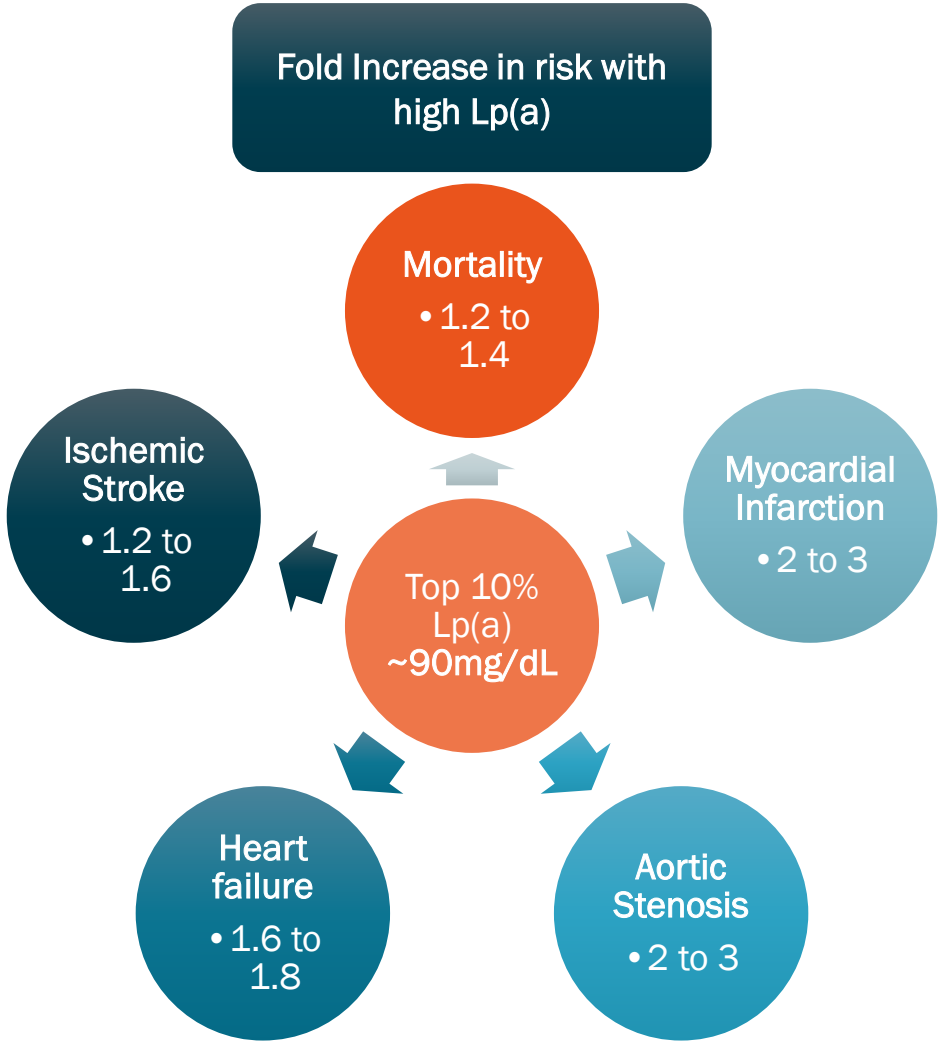
Lp(a): lipoprotein(a)

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Cardiovascular Event Risk Increases with High Lp(a)

Risk Ratio:

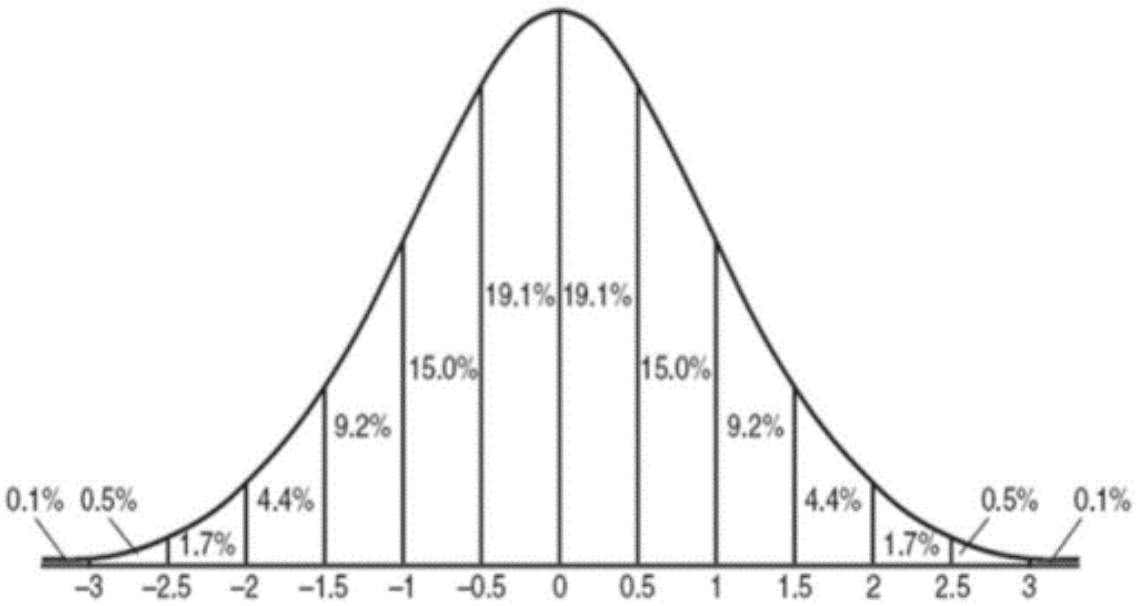
- The probability of one outcome versus another.
- A risk ratio of 2 is double the risk.
- A risk of 0.5 is half the risk



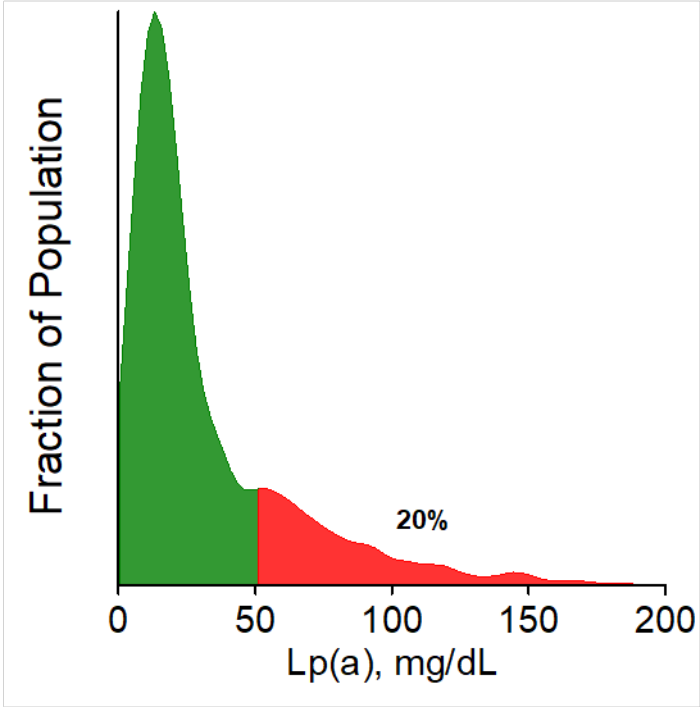
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Lp(a) Distribution in the Population

Most biological entities show a normal distribution in a population



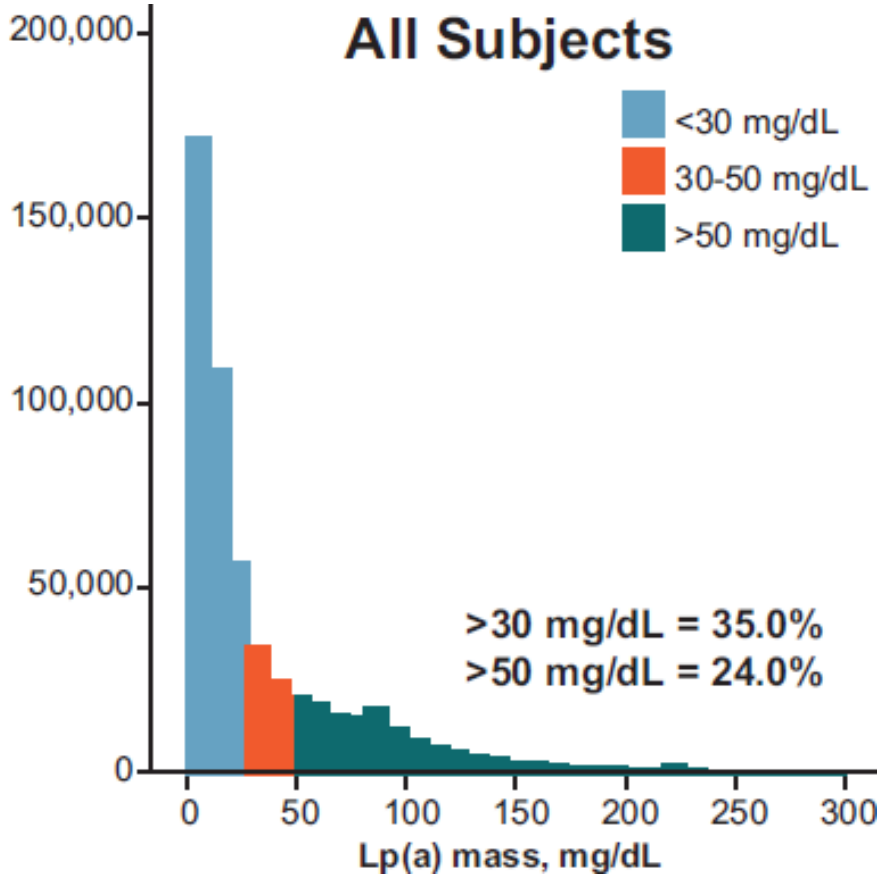
Lp(a) distribution is skewed with 20% of the population with higher than 50 mg/dL



Nordestgaard B Eur Heart J: 2010 31:2844

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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]

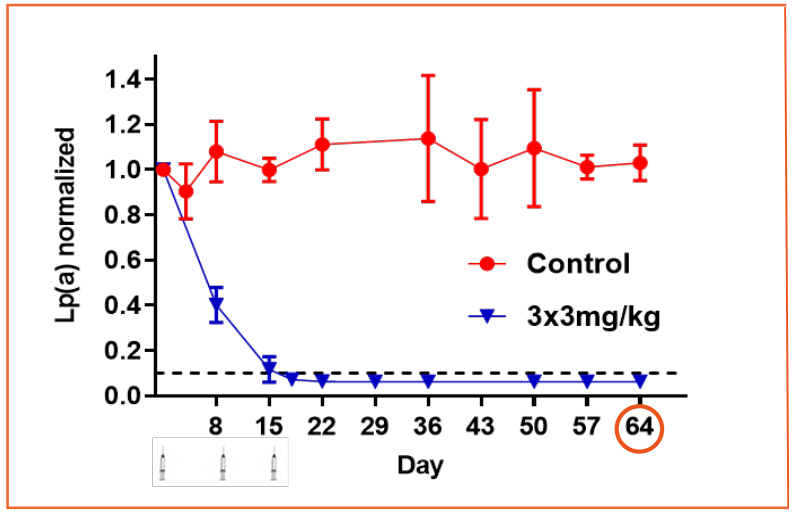
Prevalence	20%	10%	5%	1%
Lp(a) [mg/dL]	*60*	*90*	*116*	*180*
USA	64	30	16	3.2
EU	150	75	37.5	7.5
Globally	1400	700	350	70

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

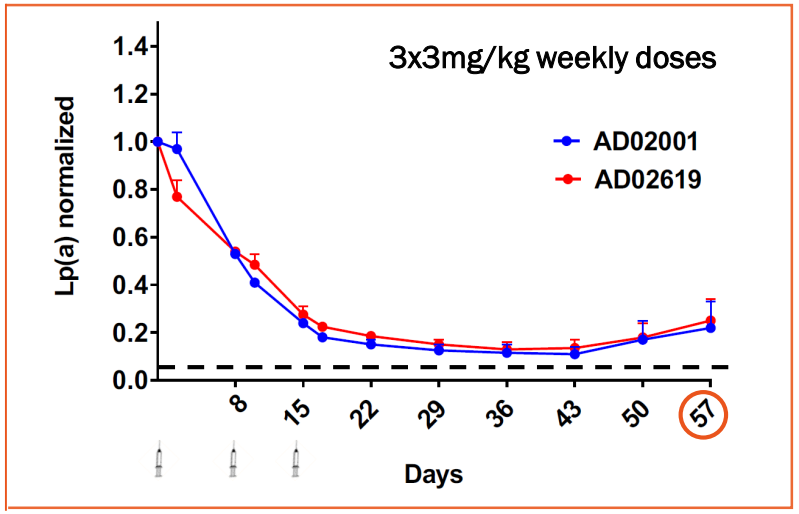
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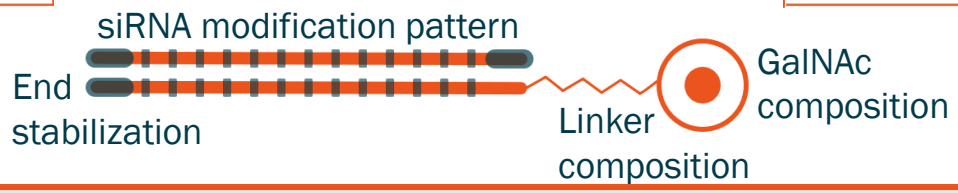
SLN360 Demonstrated Highly Competitive Preclinical Profile – More Robust Knockdown and Longer Lasting

SLN360 (wholly owned by Silence)



AMG 890 (Amgen / Arrowhead)





- **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

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

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SLN124
for the treatment of

Iron Overload Disorders



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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

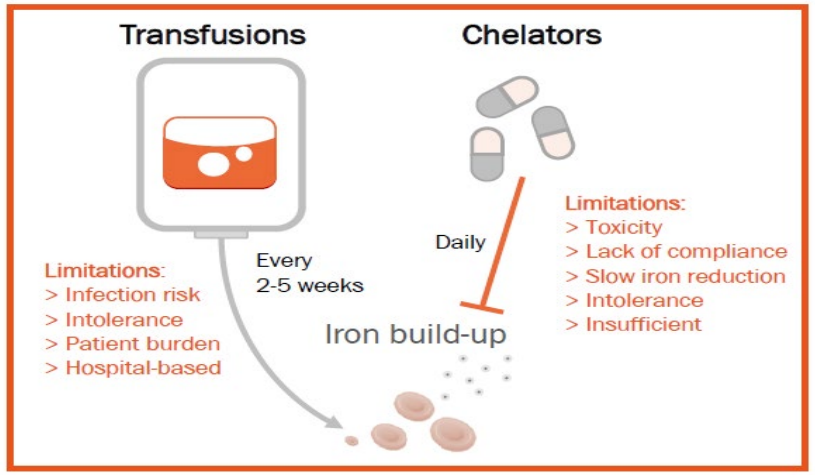
MDS[3]

>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

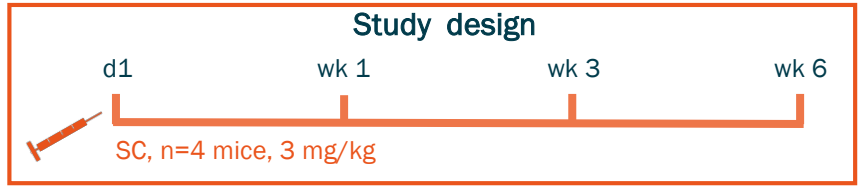
Advantages v Competition

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

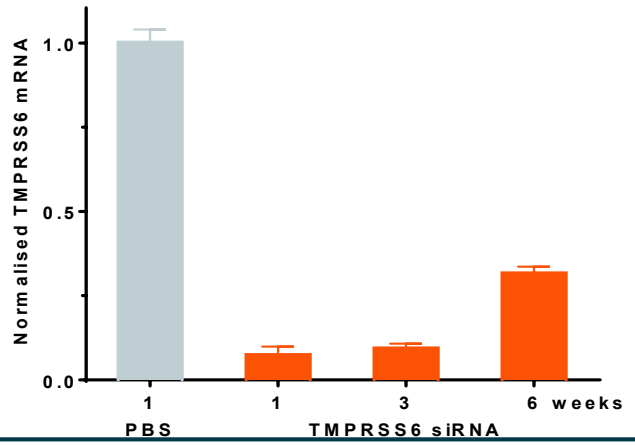
Notes: 1 TDT = Transfusion Dependent Thalassemia 2 NTDT = Non Transfusion Dependent Thalassemia 3 MDS = Myelodysplastic Syndrome

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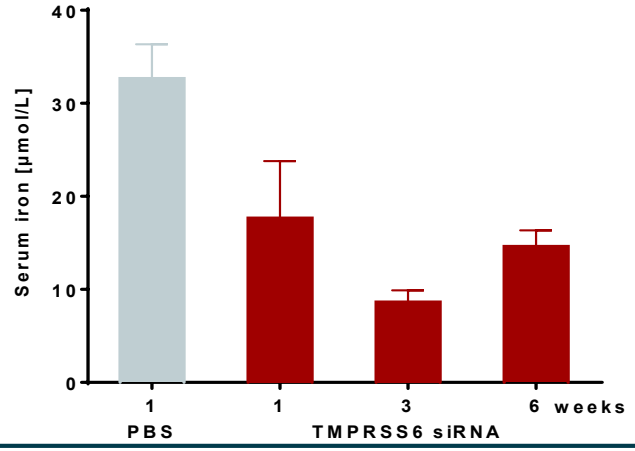
SLN124 Lowered Iron levels for at Least 6 Weeks After Single Administration in Animal Model



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

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

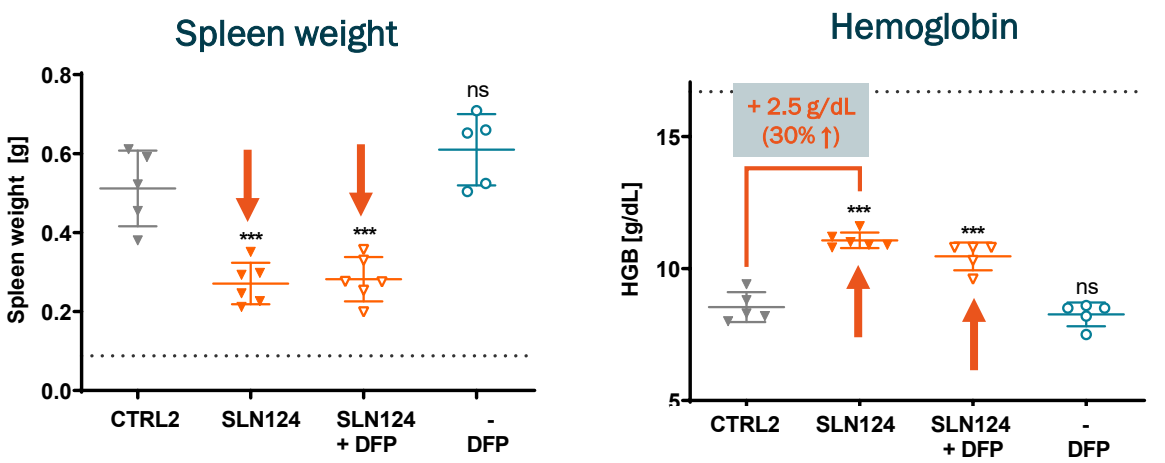
Study design

$Hbb^{th3/+}$ 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

HUDSON INSTITUTE OF MEDICAL RESEARCH



DFP = Deferiprone; CTRL2 = control siRNA

Levels of PBS-treated wild-type mice

- **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

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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

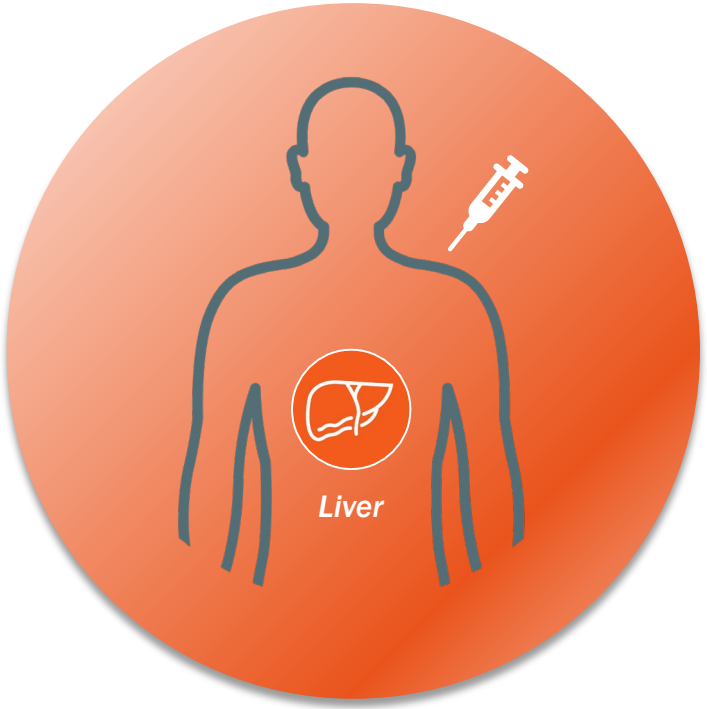
Note: all programmes are at potential risk of delay due to COVID-19

★ = data milestone

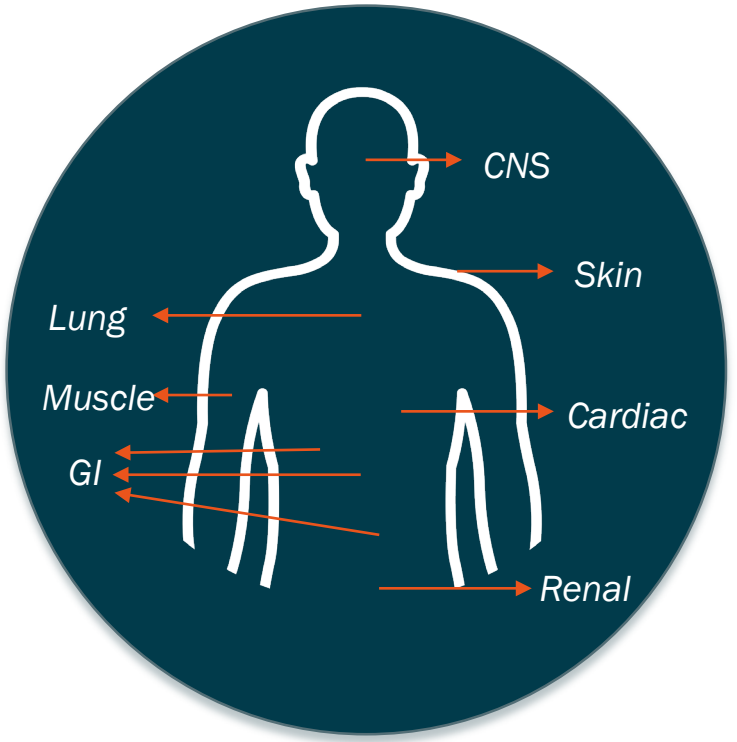
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Developing a New Extra-Hepatic siRNA Delivery Platform

Present



Future



Tap into the huge opportunity to silence genes outside of the liver

CNS: central nervous system; GI: gastrointestinal

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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)

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Flexible GalNAc siRNA platform	> GalNAc siRNA targets genetic diseases expressed in liver cells > >7,000 proteins expressed in the liver
Broad Pipeline	> Mix of wholly owned clinical programmes and partnered programmes > Advancing two wholly owned clinical programmes with expected data readouts next year • SLN360 targeting high and prevalent unmet need in cardiovascular disease • 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
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HQ in London



R&D in Berlin



+ New office in New York

Approx. 70 employees across all sites

*As of 6th November 2020

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