SILENCE THERAPEUTICS

39th Annual Cowen Health Care Conference

11 March 2019

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Silence Therapeutics' Summary

Valuable Platform	• Reproducible, proprietary gene silencing (RNAi) therapeutics platform, rapidly generating internal pipeline and diversifying out-licensing options
Haematology	• SLN124 (beta-thalassemia & MDS[1]) to enter the clinic in 2019, with first patient dosed in H2, after promising data in animal models
Strong Experienced Team	• Over 15 years of tenured oligonucleotide R&D expertise; growing clinical team, and experienced biopharma management team
Target Selection	• Focused on targeting indications in rare diseases & large population targets, including new medicine for cardiovascular disease (SLN360)
Strong Financial Position	• $35m of cash[2] extends runway to key clinical milestones such as interim results from the SLN124 Phase 1b trial.

HQ in London



R&D in Berlin



Approx. 50 employees across both sites

Notes: 1 MDS = Myelodysplastic syndrome
2 As of 31st Dec 2018
and £=$1.3

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Full Year Results – Highlights

Operational Highlights

- Lead candidate SLN124 granted Orphan Drug Designation by the European Medicines Agency for the treatment of β-Thalassemia
  - CTA filing expected shortly
  - First patients expected to enter a Phase Ib study in H2 2019
- SLN360, an Lp(a) targeting siRNA for cardiovascular disease advanced and has since started IND-Enabling studies in Feb 2019
- Out-licenced programme, QPI-1002, for Prevention of Acute Kidney Injury progressed to Phase III clinical trial by partner Quark Pharmaceuticals, Inc.
- New leadership in place with the recruitment of Dr David Horn Solomon, an experienced public company biotech CEO and board member as Chief Executive Officer
- Settlement and License Agreement with Alnylam Pharmaceuticals for tiered royalty on net sales of ONPATTRO™ in the EU

Financial Highlights

- Loss after tax of £18.4 million (2017: £1.6 million). 2017 losses were lower due to c.£9 million of gains on disposal of Arrowhead shares, and a one-off foreign exchange credit of £1.3m. 2018 also included exceptional expenditure relating to legal proceedings, with total legal fees of £4 million (2017: £1 million).
- Cash and cash equivalents and term-deposits of £26.5 million (2017: £42.7 million)
- Net cash outflow from operating activities £16.8 million (2017: £9.6 million)

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Experienced Leadership Team

Deep Background in Discovery & Development of RNA Therapies With Strong Biopharma Experience



David Horn Solomon
CEO & President CEO

ZEAL & ZEALAND PHARMA

COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS

Since 2018



Marie Wikstrom Lindholm
VP Technology Innovation

santaris pharma a/s

Roche

Since 2018



Rob Quinn,
Interim CFO

gsk

Deloitte.

Since 2017



Richard Jenkins
VP Clinical Development

Takeda

gsk

Since 2018



Laura Roca-Alonso, Ph.D.
VP Corporate Development

Imperial College London

UCL

Since 2014



Michael Mulqueen,
VP BD & Licensing

BIOTIE THERAPIES

Roche

Since 2017



Linnea Elrington,
VP Human Resources

GLORY

cisiv

Since 2017

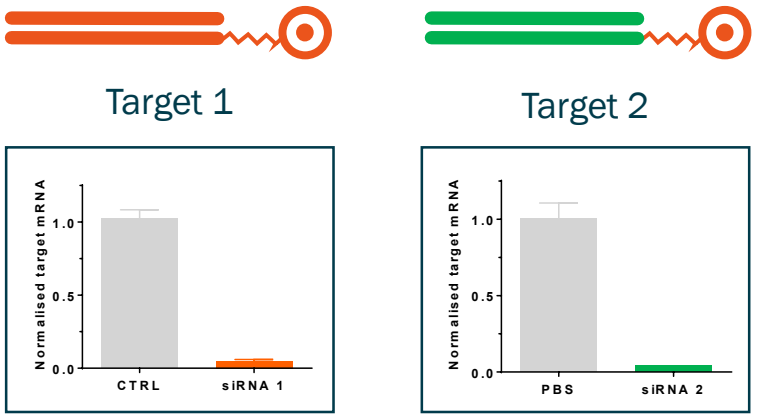
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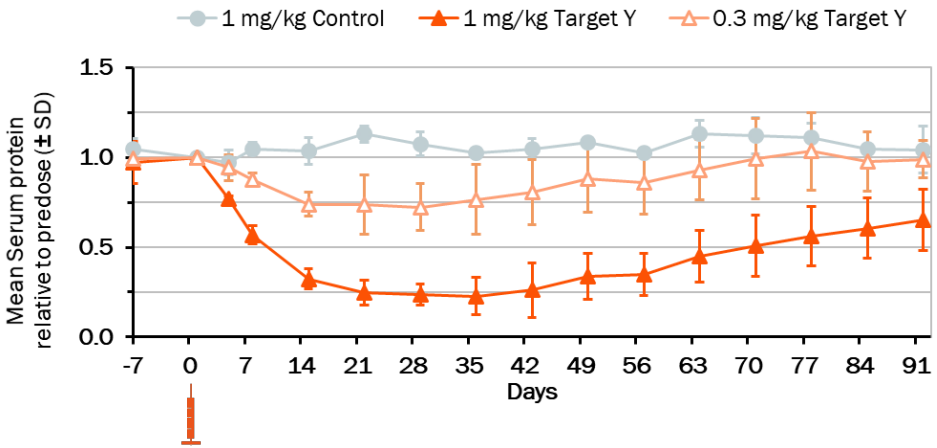
Reproducibly silencing disease-associated genes using our proprietary platform technology

Platform technology with freedom to operate: GalNAc-siRNA, able to mediate highly specific gene silencing in hepatocytes (liver) – "Specificity upon specificity"

Patient friendly: Subcutaneous delivery and infrequent dosing (monthly or longer). Well tolerated.

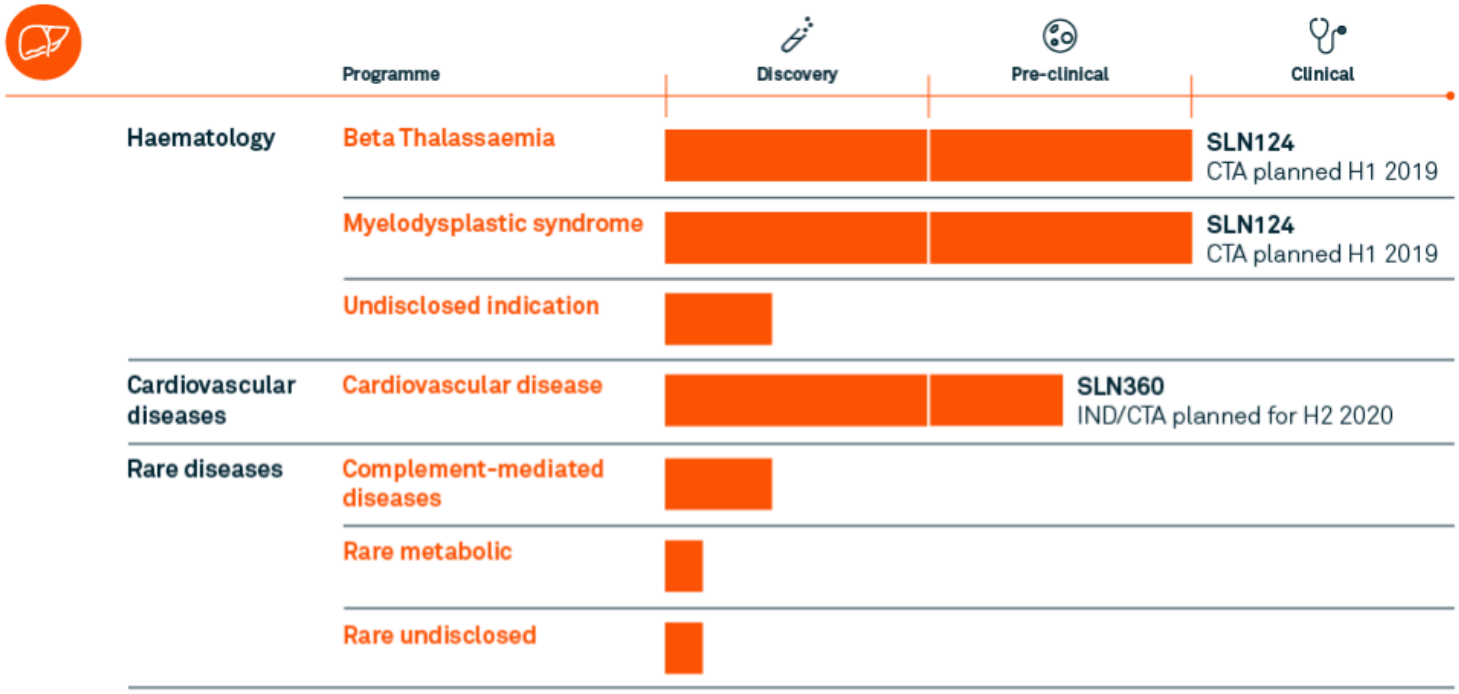
~7,000 genes operate in the liver. Silence can target any of them by adapting the siRNA sequence, using the same technology.



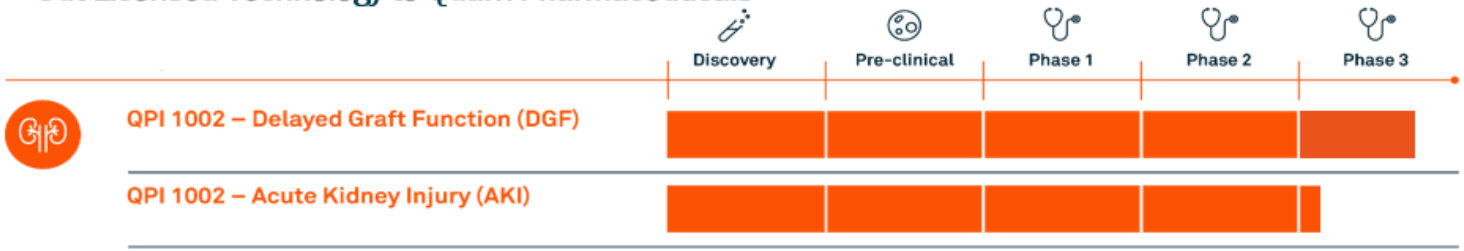


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Our Pipeline



Out-Licensed Technology to Quark Pharmaceuticals



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SLN124

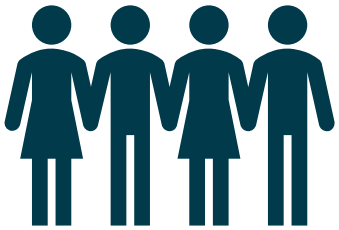
for the treatment of

Iron Overload Disorders

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Market Opportunity of SLN124

US and EU patients



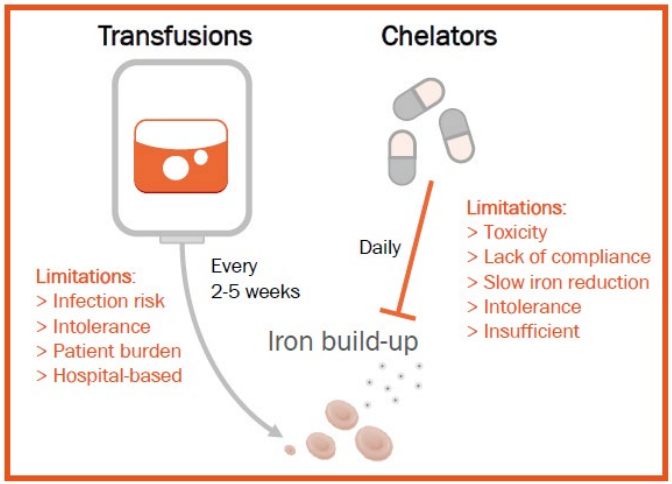
β-Thalassemia

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

MDS[3]

>100,000

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

- Quality of Life
- Safety
- Organ iron levels
- Compliance
- Less frequent dosing

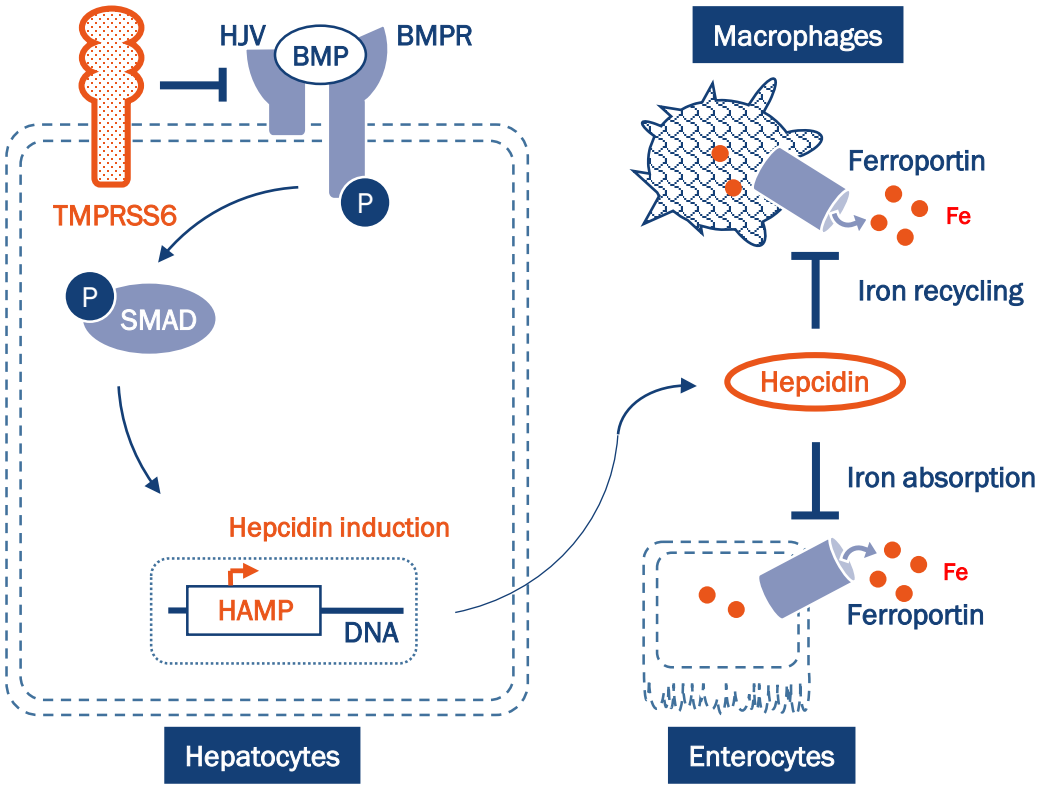
Competition

- SoC: Transfusions + Chelators
- Antisense RNA
- Luspatercept
- Gene therapy
- Hepcidin mimetics

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

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SLN124 Mechanism of Action: Increasing Hepcidin by Silencing its Repressor TMPRSS6



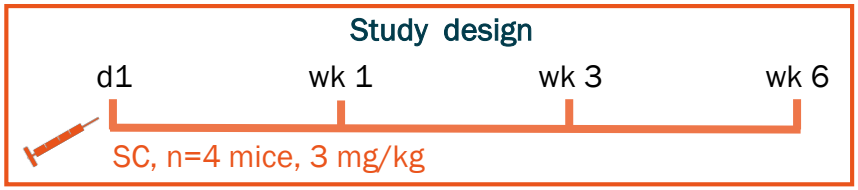
- TMPRSS6 (Transmembrane Protease, Serine 6) is a negative regulator of the BMP/SMAD signaling pathway
- Inhibition of TMPRSS6 in hepatocytes induces Hepcidin expression
- Hepcidin reduces absorption of dietary iron and the release of iron from cellular storage, thereby reducing circulatory iron levels
- The liver is the predominant source of Hepcidin

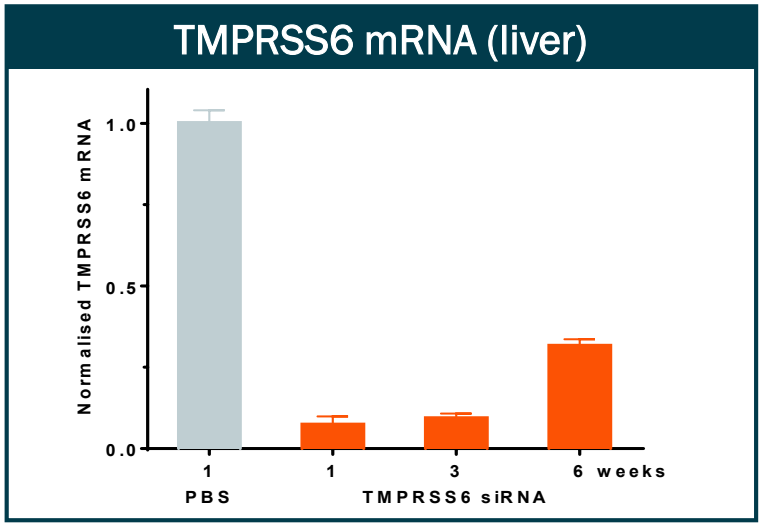
Silencing TMPRSS6

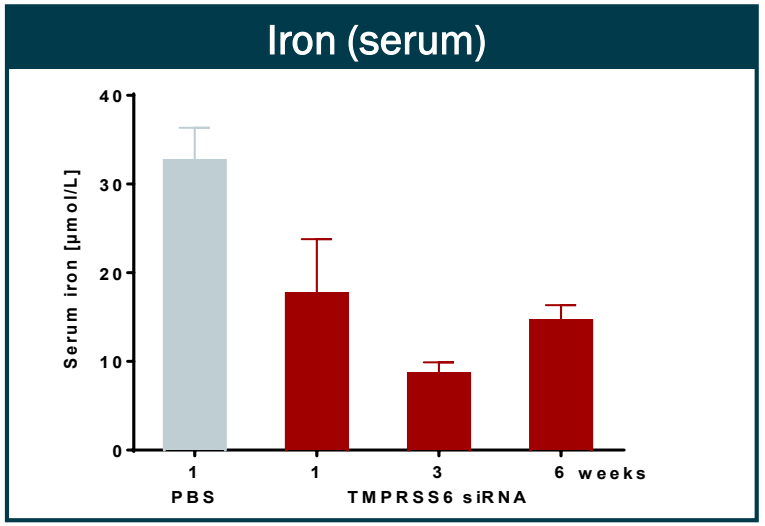
1. Increases Hepcidin levels
2. Reduces iron levels
3. Improves erythropoiesis
4. Reduces anemia & iron overload

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SLN124 Lowers Iron Levels for at Least 6 Weeks after Single Administration in Mice







- 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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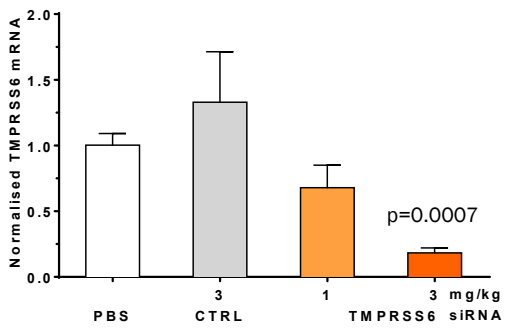
Therapeutic Activity of SLN124 in a Disease Model of Hereditary Haemochromatosis ($HFE^{-/-}$ mice)

Collaboration with
Prof. Dr. Martina Muckenthaler
Heidelberg University, Germany

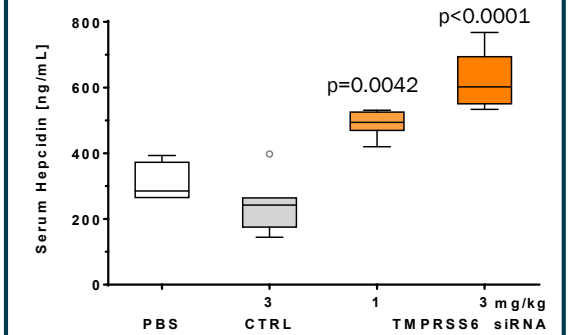
Study design



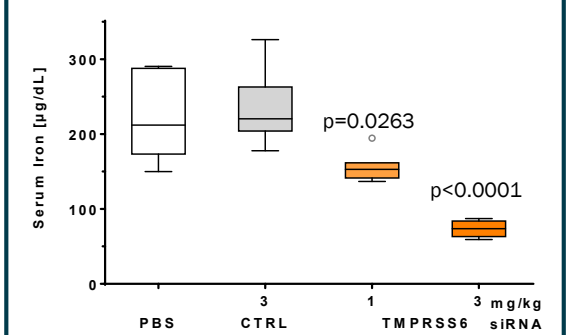
TMPRSS6 mRNA (liver)



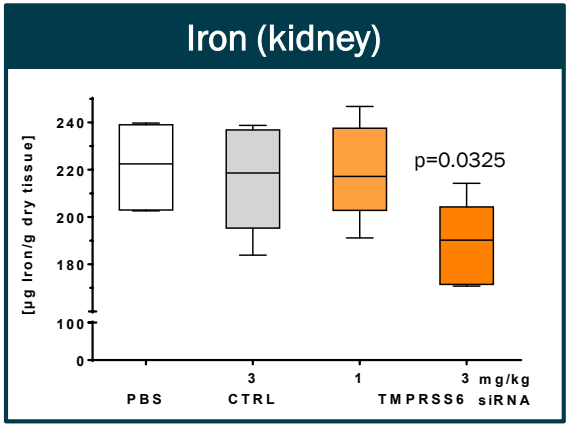
Hepcidin (serum)



Iron (serum)



Iron (kidney)



- Dose-dependent and robust silencing of TMPRSS6 mRNA in the liver
- Increase in serum hepcidin levels
- Reduction of serum and kidney iron levels to physiological values

Kruskal-Wallis test with uncorrected Dunn's test against non-targeting control CTRL

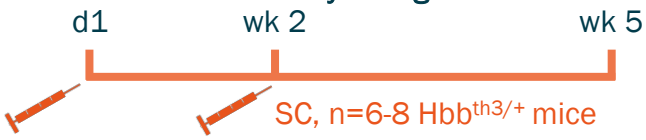
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SLN124 Reduces ROS and Improves RBC Parameters in a β-Thalassemia Disease Model

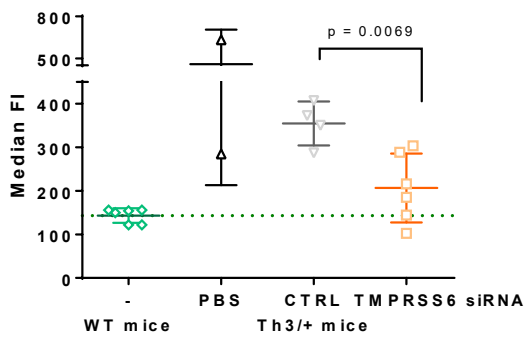
Collaboration with
Prof. J. Vadolas & Dr. Grigoriadis
Monash Medical Centre/Melbourne, Australia

HUDSON INSTITUTE OF MEDICAL RESEARCH

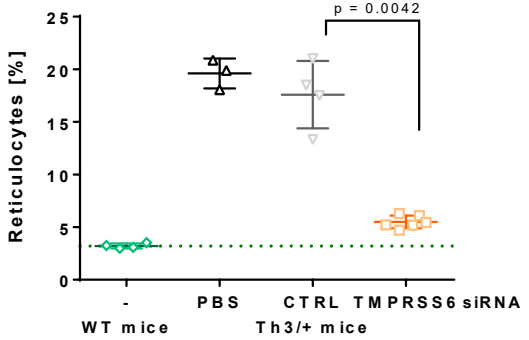
Study design



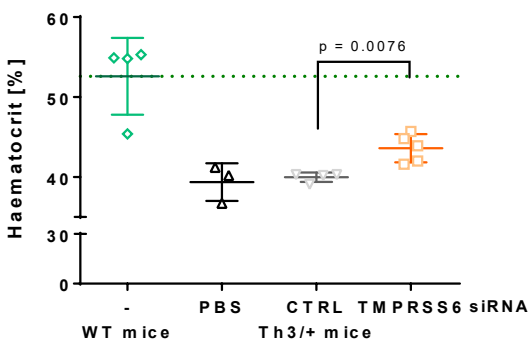
Reactive oxygen species (ROS)



Reticulocyte proportion



Haematocrit



- Reduction of ROS to levels in healthy mice
- Normalisation of reticulocyte proportion and improvement of haematocrit
- SLN124 significantly improves erythropoiesis in animal model for β-Thalassemia intermedia

ROS = reactive oxygen species; RBC = red blood cells

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We are Planning to Initiate a Multicentre, Randomised, Placebo Controlled Phase 1b in 2019

This is a two part first-in-human, multicenter, randomized placebo controlled single ascending and multiple dose study to assess the preliminary safety, tolerability, PK and efficacy of SLN124 administered subcutaneously for the treatment of non-transfusion dependent thalassemia and low risk myelodysplastic syndrome.

Study design

> Part A:

- Single dose escalation study to evaluate the dose response to SLN124 with a view to identify the most appropriate dose to bring forward into the multiple dose portion of the study
- Primary aim to determine the safety and tolerability of SLN124 for the treatment of non-transfusion dependent β-thalassemia

> Part B:

- Bring forward the most efficacious and best tolerated dose to evaluate multiple administrations of SLN124 on hematinic parameters in patients with β-thalassemia and MDS
- Primary aim to determine the safety and tolerability of multiple doses of SLN124 for the treatment of non-transfusion dependent β-thalassemia and low risk myelodysplastic syndrome

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SLN124 Summary

- **Preclinical package**: Robust data generated in several disease models.
- **Status:** Non-clinical development work ongoing, with CTA filing expected in Q2 2019. Orphan Designation granted for β–Thalassaemia and application planned for MDS.
- **Clinical plans:** Phase 1b planned in patients (β–Thalassaemia and MDS). Network of KOL's established.
- **Dosing regimen:** Patient-friendly, with monthly or less frequent dosing expected and subcutaneous administration route.
- **Regulatory**: Positive feedback received at Scientific Advice meetings with both the UK (MHRA) and German (BfArM) national regulators.
- SLN124 is well positioned for **commercial success** against current standard of care and other medicines in development.

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SLN360

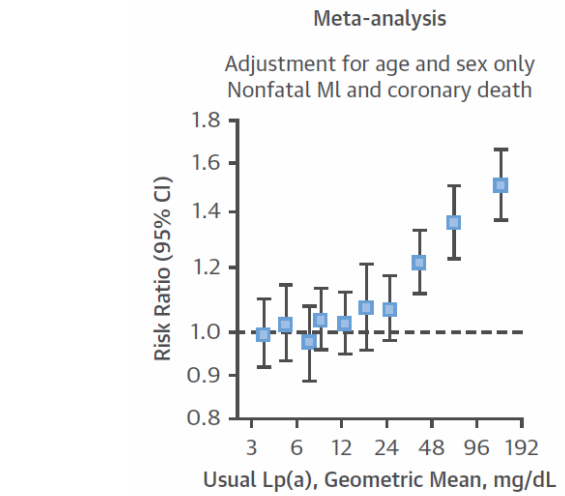
for the treatment of

Cardiovascular disease with high Lp(a)

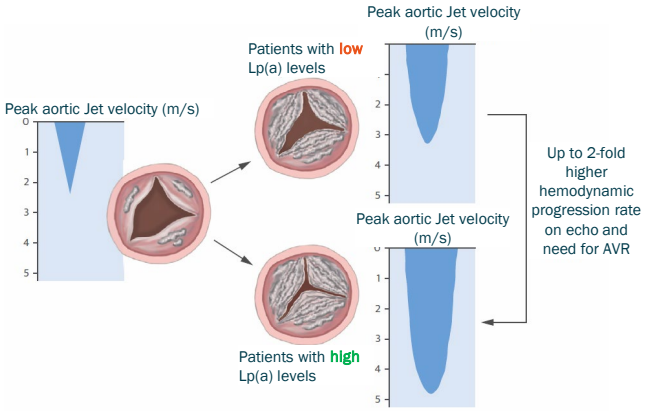
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SLN360 targets Lp(a) - an Independent Risk Factor for CVD

- Lp(a) is a lipoprotein involved in the transportation of lipids.
- Lp(a) is a validated target in humans. Lp(a) excess is detected in patients with premature CVD:
  - High Lp(a) is associated with CHD, unstable angina, myocardial infarction (MI) and other CVD complications
  - High Lp(a) levels have been shown to predict a 2-4 fold increase in risk of MI and CVD
  - Adding Lp(a) levels ≥80th percentile to conventional risk factors improves MI and CHD risk prediction
- Lp(a) is only minimally confounded by typical risk factors such as smoking, blood pressure or diabetes.
- High unmet need - Apheresis is the only approach that can reduce Lp(a) levels by a large amount, however is invasive and burdensome: procedure lasts 70min-2h, can be performed up to every week



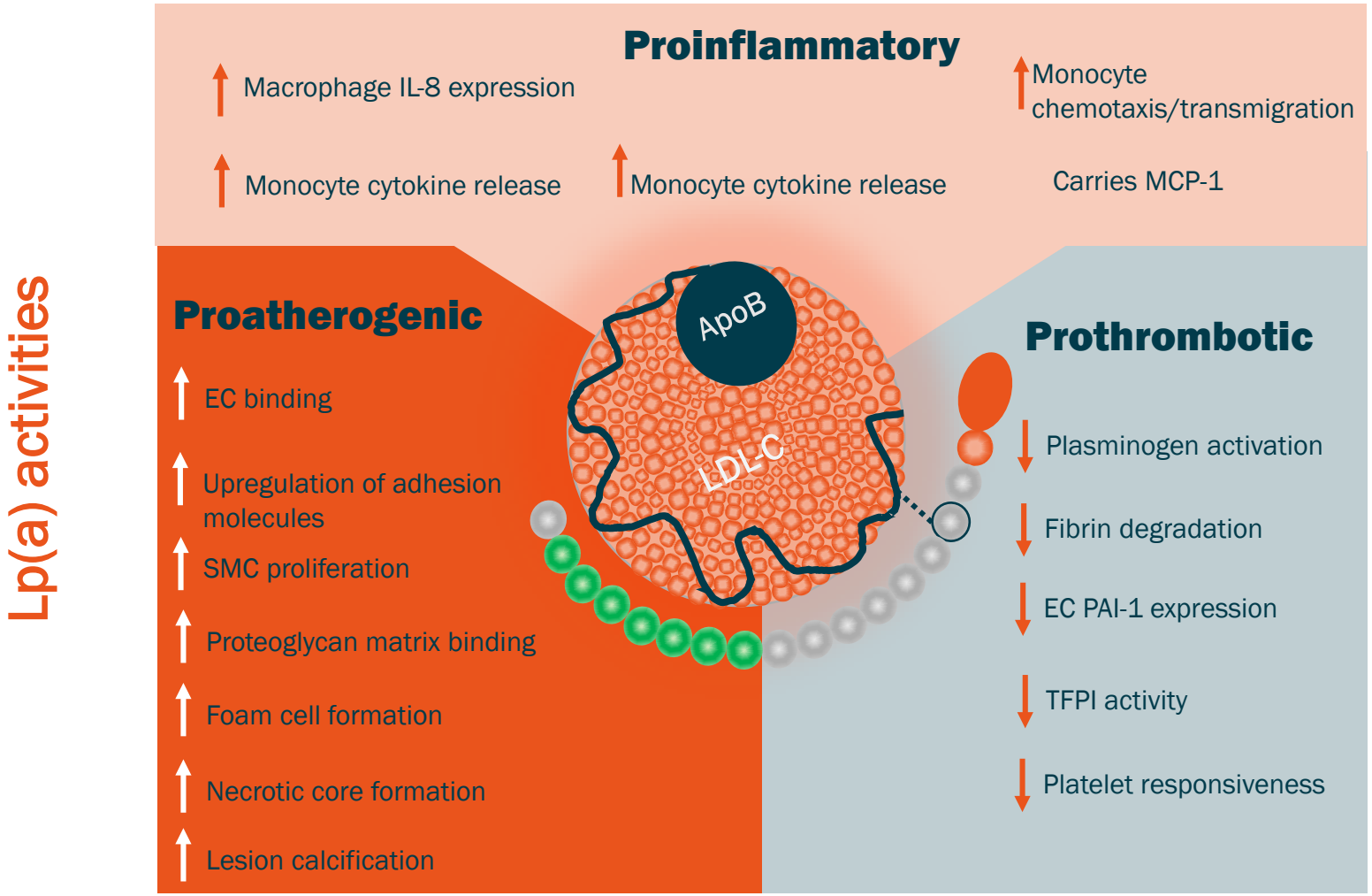
Adjustment for additional risk factors does not produce dramatic changes



Tsimikas 2017

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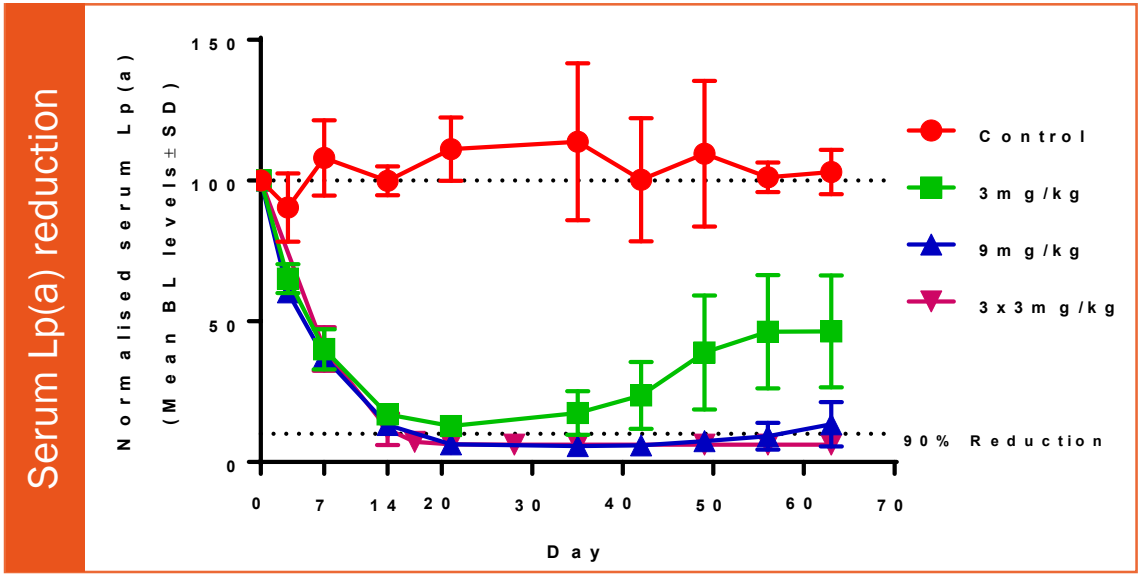
Lp(a) has Prothrombotic, Proinflammatory and Proatherogenic Properties

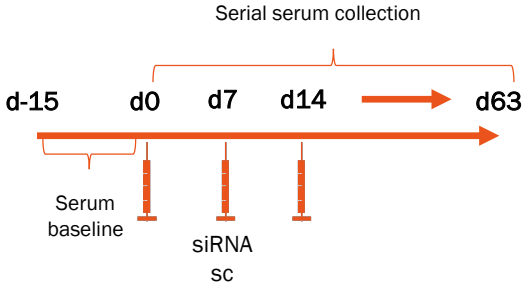


Adapted from Tsimikas et al 2017

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Proof of mechanism achieved





Group	mg/kg	Days
1	0	0
2	3	1
3	9	1
4	3	1, 7, 14

Prolonged serum knockdown of Lp(a)

> Multiple dosing at 3mg/kg resulted in sustained reduction of Lp(a) serum levels (>90%) for at least over two months after first dose (max ~>95% KD)

> Similar outcome after single subcutaneous injection of SLN360 at 9mg/kg.

> Over 85% KD at NADIR for single 3mg/kg injection with 50% KD still observed after 2 months post treatment

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SLN360 summary

Rationale

> Lp(a) is a low-density lipoprotein produced predominantly by the liver and composed of Apo(a) and Apo B, both hepatocyte expressed genes.

> Genetically defined high Lp(a) serum levels are unaffected by diet and exercise and are an independent risk factor for CVD. There is no specific Lp(a) targeting therapy available at the moment.

> An *LPA* silencing siRNA would provide a specific, safe and durable approach for reducing Lp(a) levels in high risk patients.

Our Programme

> A potent lead sequence has been selected and tested *in vivo* in non-human primates (NHP).

> Proof of mechanism has been achieved in NHP: dose dependent reduction in both LPA (liver mRNA) and Lp(a) (serum protein) observed, with max 95% KD observed after multiple dosing.

> Our drug compares positively against published data by competitors, suggesting a superior performance.

> **IND/CTA is planned for H2 2020**

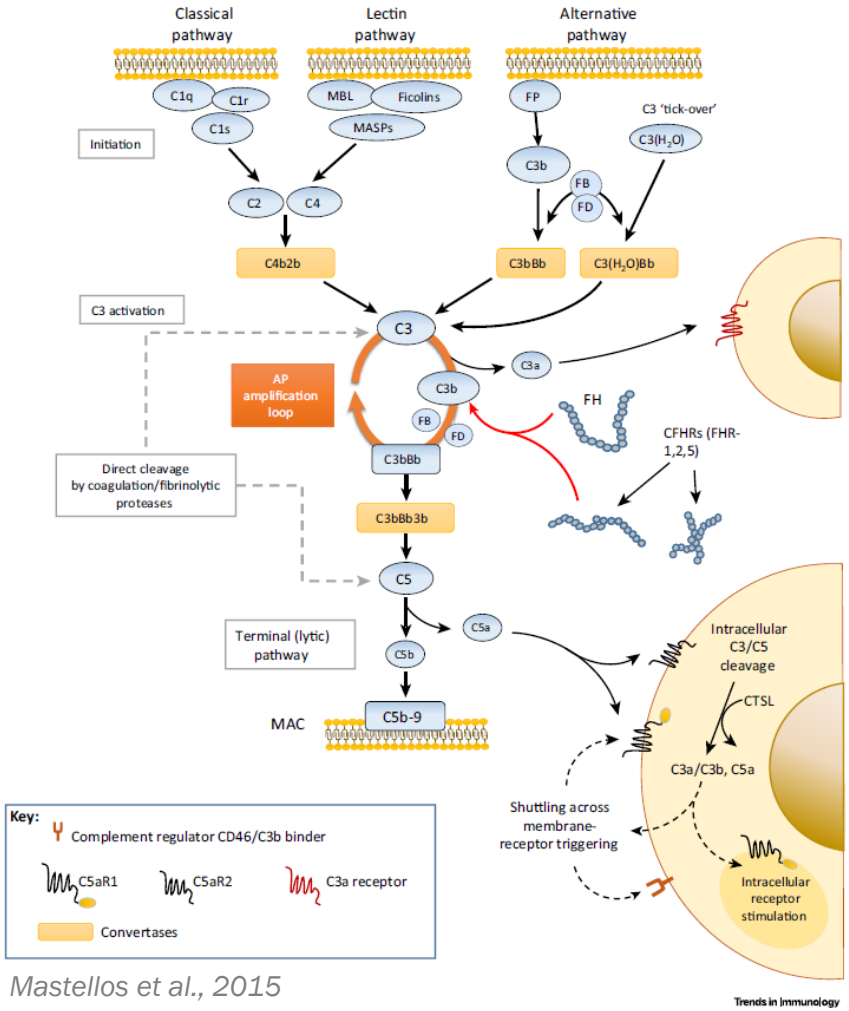
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Complement-Mediated Diseases

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GalNac siRNAs for the treatment of Complement-mediated diseases

Schematic overview - complement system



Mastellos et al., 2015

Targeting the complement system offers a broad indication spectrum (such as Paroxysmal Nocturnal Hemoglobinuria, Myasthenia gravis, C3 Glomerulopathy, atypical Hemolytic Uremic Syndrome or Cold Agglutinin Disease)

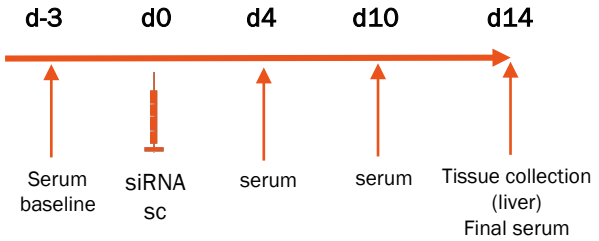
- **The Complement system** is part of the innate immune system and consists of 3 pathways
- > 30 serum proteins (many thereof produced in hepatocytes)
- It represents an activation cascade with various effector functions, such as MAC (membrane attack complex) formation for pathogen destruction and activation of immune cells
- First drug on the market targeting the complement pathway is Eculizumab (Soliris, C5 Ab)
- **There is unmet need** because Eculizumab is not consistently effective for all patients (mutations, non responders) and indications

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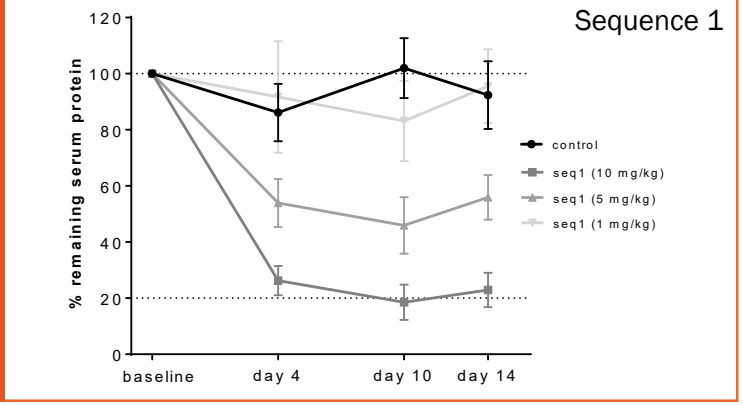
Complement-mediated diseases
Initial results: Proof of Mechanism in vivo (mouse)

> **Study design:**

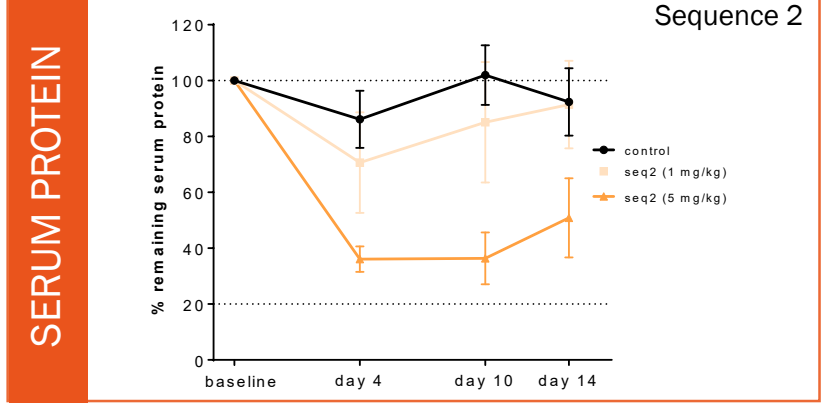
- n=4 healthy mice per group, serum sampling at day -3, 4, 10 and 14, liver tissue at day 14
- siRNAs: **non-optimized** GalNac conjugated chemistry



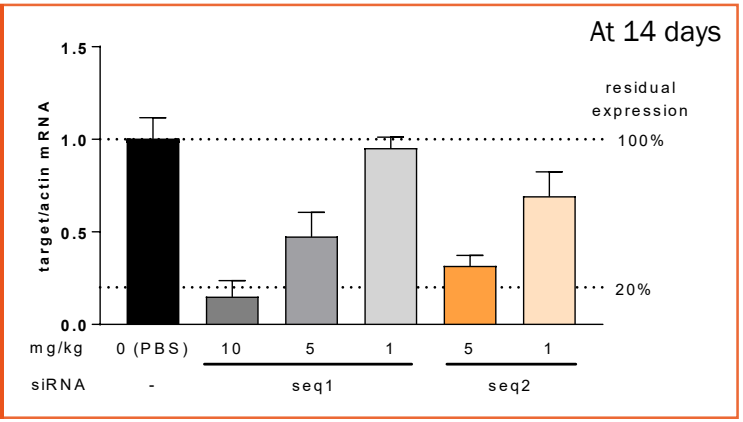
SERUM PROTEIN



SERUM PROTEIN



RNA



Target knock down:
> 80 % mRNA & protein knock down achieved using non-optimized siRNAs

→ Identification of 2 potent siRNA sequences for lead optimization and NHP studies (using advanced chemistry)

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Summary & Outlook

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Expected Newsflow & Company Milestones

	H1 2019	H2 2019	2020
SLN124			
File CTA	X		
First In Human Dosing		X	
First Interim Results			X
SLN360			
Clinical candidate nomination	X		
IND/CTA filing			X
2018 New Targets			
pPOC in mice	X		
Clinical candidate nomination		X	
Platform Strengthening			
Gen4 toolbox validation and in use	X		
Quark Out-License in QPI-1002			
First interpretative results for DGF Phase 3 study expected	X		

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Silence Therapeutics' Summary

Valuable Platform	• Reproducible, proprietary gene silencing (RNAi) therapeutics platform, rapidly generating internal pipeline and diversifying out-licensing options
Haematology	• SLN124 (beta-thalassemia & MDS[1]) planning to enter the clinic in H2 2019 after promising efficacy signals in animal models
Strong Experienced Team	• Over 15 years of tenured oligonucleotide R&D expertise; growing clinical team, and experienced biopharma management team
Target Selection	• Focused on targeting indications in rare diseases & large population targets, including new medicine for cardiovascular disease (SLN360)
Strong Financial Position	• $35m of cash[2] extends runway to key clinical milestones such as interim results from the SLN124 Phase 1b trial.

HQ in London



R&D in Berlin



Approx. 50 employees across both sites

Notes: 1 MDS = Myelodysplastic syndrome
2 As of 31st Dec 2018
and £=$1.3

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Q&A