SILENCE THERAPEUTICS

Non-confidential presentation

Cantor Fitzgerald Global Healthcare Conference, New York

October 3rd, 2018

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Silence Therapeutics' Summary

Valuable Platform	> Reproducible, proprietary RNAi therapeutics platform, rapidly generating internal pipeline and diversifying out-licensing options
Haematology	> SLN124 (Beta-Thalassemia & MDS) 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 in Berlin; growing clinical team, and experienced management team in London
Target Selection	> Focused on targeting indications for a combination of both rare diseases and large population targets
Strong Financial Position	> $44m of cash[1] extends runway to key clinical milestones. IP licensing provides opportunity for non-dilutive funding

HQ in London



R&D in Berlin



Approx. 45 employees across both sites

Notes: 1 As of 30 June 2018 and £=$1.3

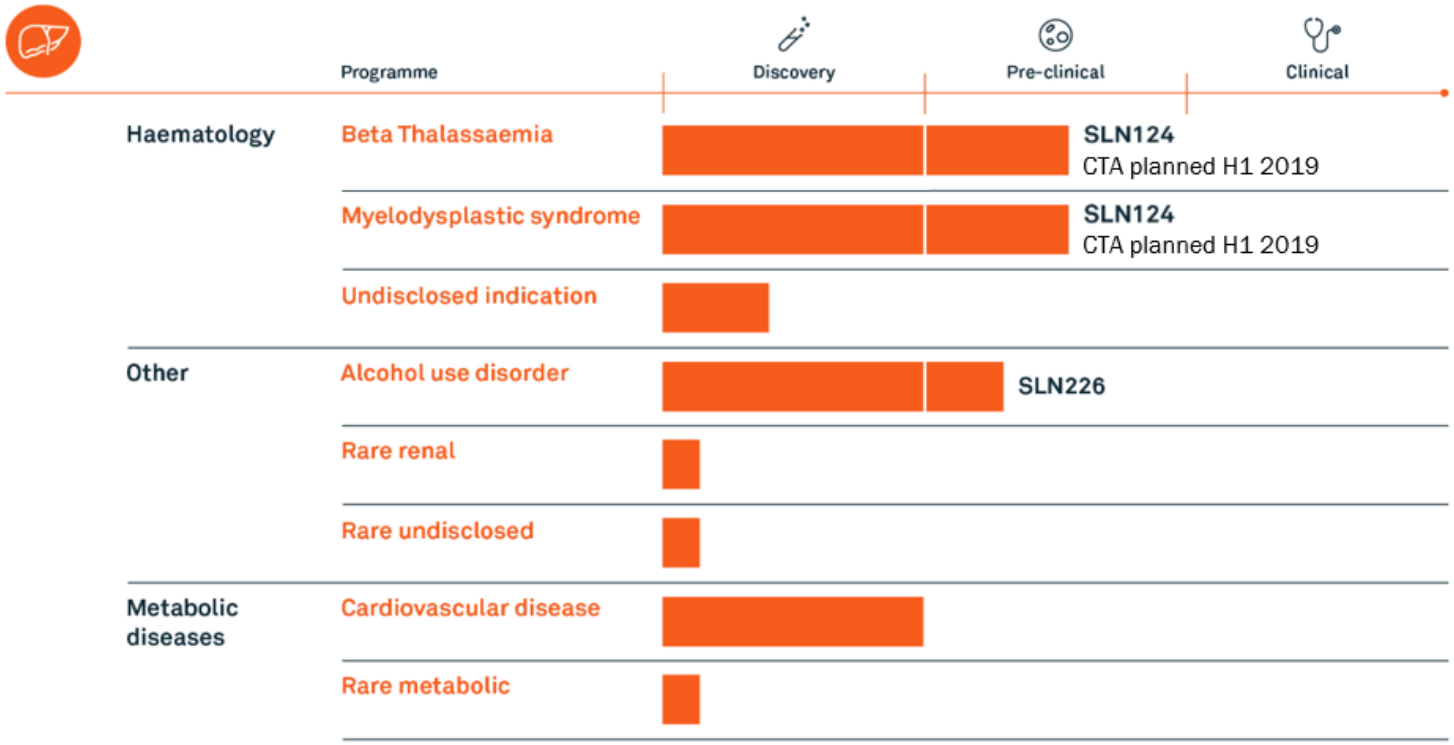
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Silence: Operational Highlights

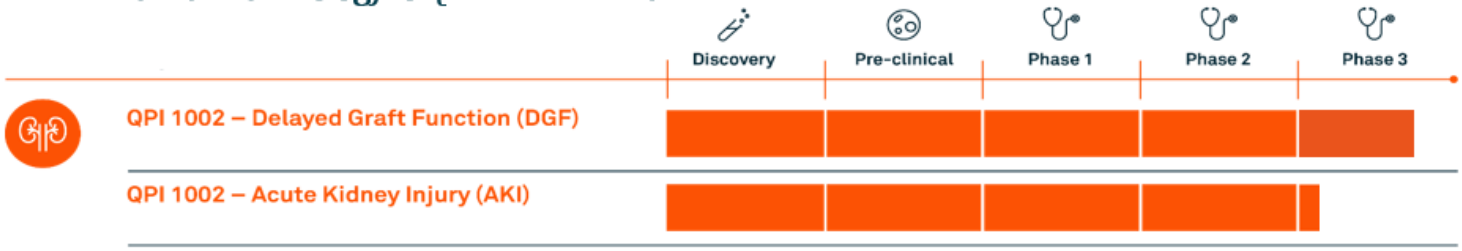
- **New leadership** in place with the recruitment of Dr David Horn Solomon as Chief Executive Officer, an experienced public company biotech CEO, board member and biotech investor.
- **The field is advancing**: Gene-silencing as a therapeutic modality was granted its first drug approval by the FDA on 10 August for *patisiran*, validating RNAi as a class of drugs that now have a clear path to market.
- **Positive regulatory feedback** and **promising data** in clinically validated animal disease models representative of iron overload disorders, increases confidence in Silence's lead candidate **SLN124**, with initiation of the Phase Ib study anticipated in H2 2019.
- Out-licenced programme, **QPI-1002** for Prevention of Acute Kidney Injury progressed to Phase III clinical trial by partner Quark Pharmaceuticals, Inc.
- **Patisiran** remains accused of infringement of Silence's Intellectual Property in the United Kingdom and Portugal.

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Our Pipeline



Out-Licensed Technology to Quark Pharmaceuticals



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Experienced Leadership Team

Strong Background in Discovery & Development of RNA Therapies



David Horn Solomon

ZEAL&
ZEALAND PHARMA

Columbia University
College of Physicians and Surgeons

Since 2018



Marie Wikstrom Lindholm
Head of Technology Innovation

santaris pharma a/s
Roche

Since 2018



David Ellam,
Chief Financial Officer

BIOMARIN
Ark therapeutics ltd.

Since 2016



Richard Jenkins
Head of Clinical Development

Takeda
gsk

Since 2018



Laura Roca-Alonso, Ph.D.
Head of Corporate Development

Imperial College London
UCL

Since 2014



Michael Mulqueen,
Head of BD & Licensing

BIOTIE THERAPIES
Roche

Since 2017



Alison Gallafent,
Head of Intellectual Property

CMS Law. Tax
gsk

Since 2017



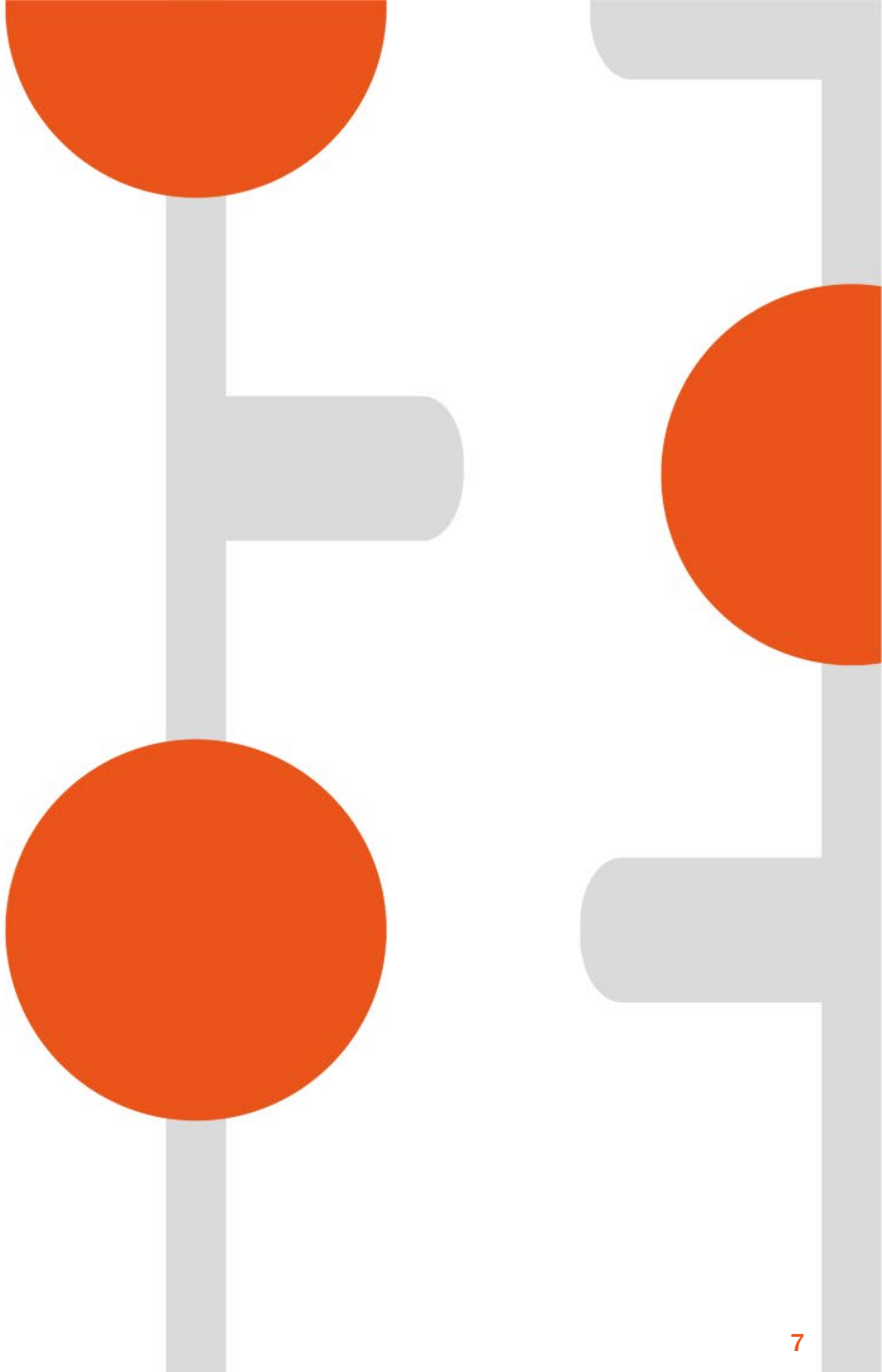
Linnea Elrington,
Head of Human Resources

GLORY
cisiv

Since 2017

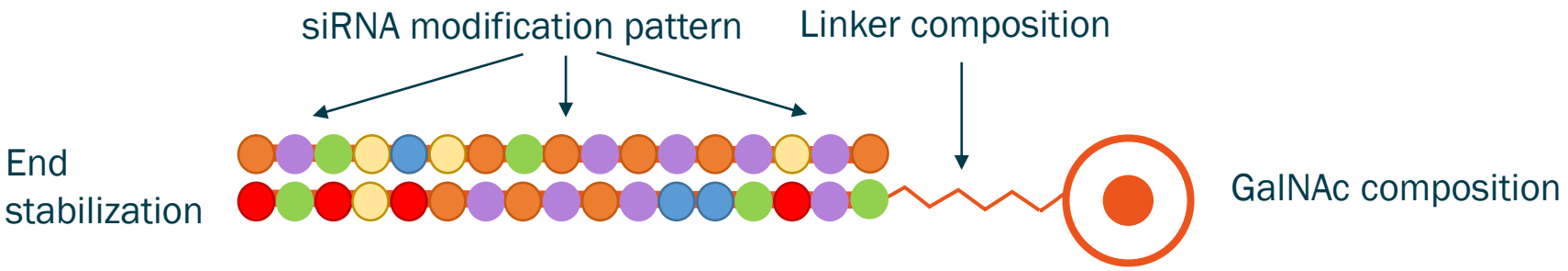
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GalNAc-siRNA Platform Technology



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Modifying Molecular Design to Enhance Performance



> Modification pattern: reduced number of non-natural modifications
> End stabilization: increased circulation half-life, activity and duration of action
> Linker: simplified synthesis, increased activity
> GalNAc: lower dosing via optimization of number & placement of monomers

> Gen 1 → Gen 2 → Gen 3 → Gen 4 →

Evolving a better molecule: Increasing activity & duration, lowering COGS and dosing

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Evolution of Our GalNAc-siRNA Platform



GEN1

2016

- Served to transition to conjugate technology, establishing baseline performance. No FTO

GEN2

2017

- Patents filed
- Clinical stage in 2019 (SLN124) and used in late pre-clinical stage programmes (SLN226, CVD)
- Robust performance, competitive to peers

GEN3

Reduced non-natural modifications

- Patents filed
- Entered pipeline in Q2 2018
- Advantages: Improved safety profile and COGS, and FTO further strengthened

GEN4

2018

Different GalNAc unit numbers and positioning

- Patents filed
- Further optimisation ongoing
- Plans to enter the pipeline in early 2019
- Advantages: improved potency, COG and safety

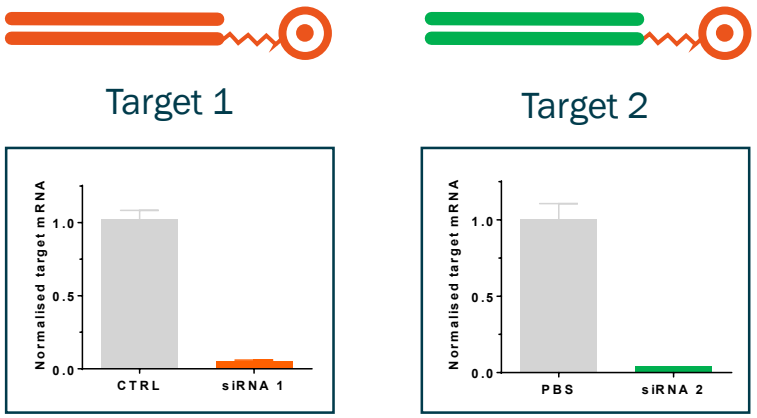
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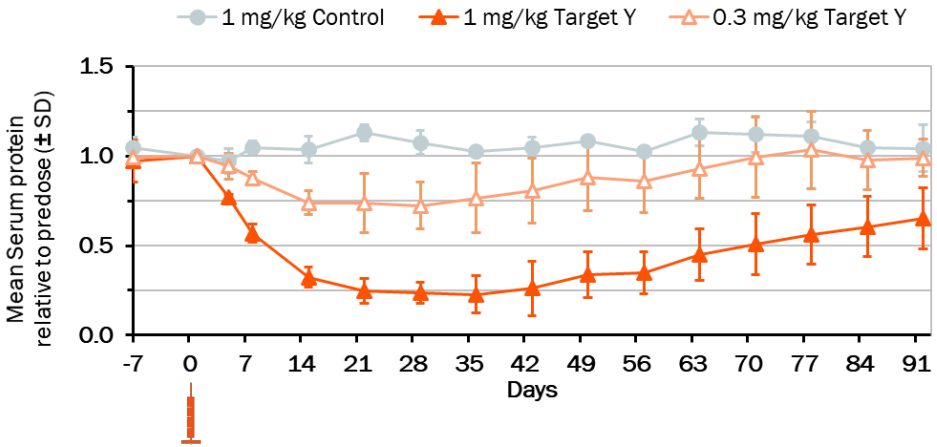
Platform Performance

Platform technology with FTO: 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.





Able to reproducibly and competitively silence disease-associated genes using our proprietary platform technology

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SLN124

for the treatment of

Iron Overload Disorders

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Treatment of Iron Overload Disorders (IOD)

GOAL

> Provide an effective and safe novel treatment option for patients with iron overload conditions with infrequent s.c. dosing

RATIONALE

> Target a key modulator in iron regulation with a GalNAc-siRNA molecule providing a **highly specific, effective & safe** option through inhibition of a disease relevant target gene (TMPRSS6) expressed in hepatocytes

CURRENT STAGE

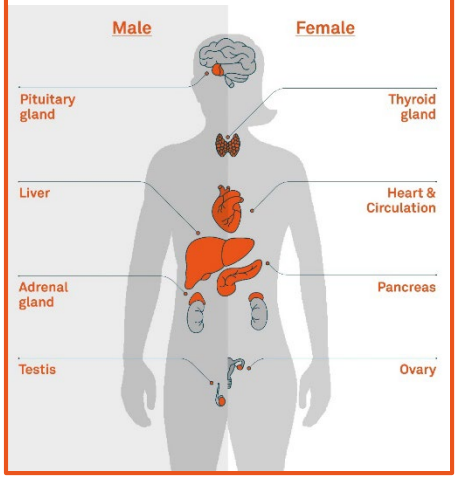
> Preclinical development with plans to enter clinical development in H2 2019 after Q2 2019 CTA filing

Iron overload disorders:

> **Myelodysplastic Syndrome (MDS)**
> **β-Thalassemia**
> Hereditary Haemochromatosis
> Aplastic Anaemia
> Sideroblastic Anaemia

If untreated, iron accumulation in organs leads to severe organ damage,

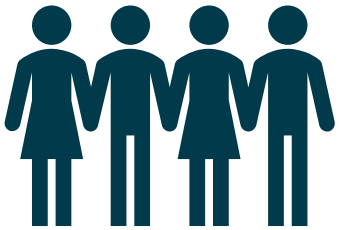
Affected organs



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Market Opportunity of SLN124

US and EU patients



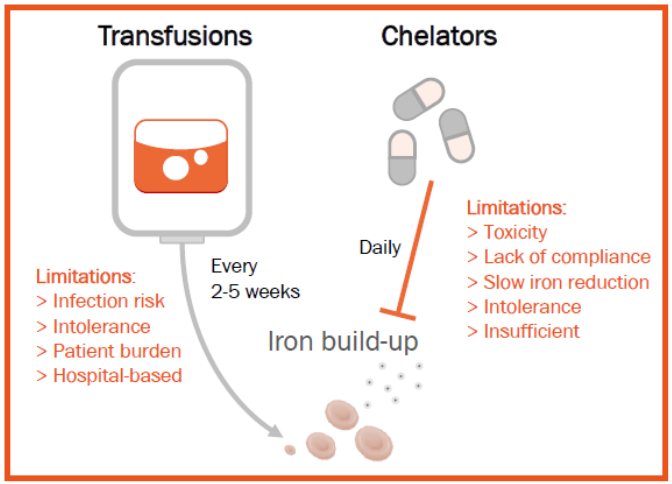
β-Thalassemia

~40,000 TDT
~20,000 NTDT

MDS

>100,000

Standard of Care



Benefits of SLN124

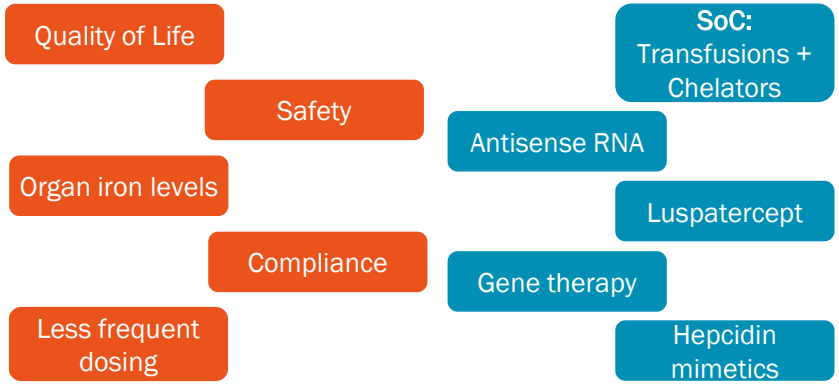
SLN124 aims to:

1. Reduce organ iron levels &
2. Enhance erythropoiesis

↓

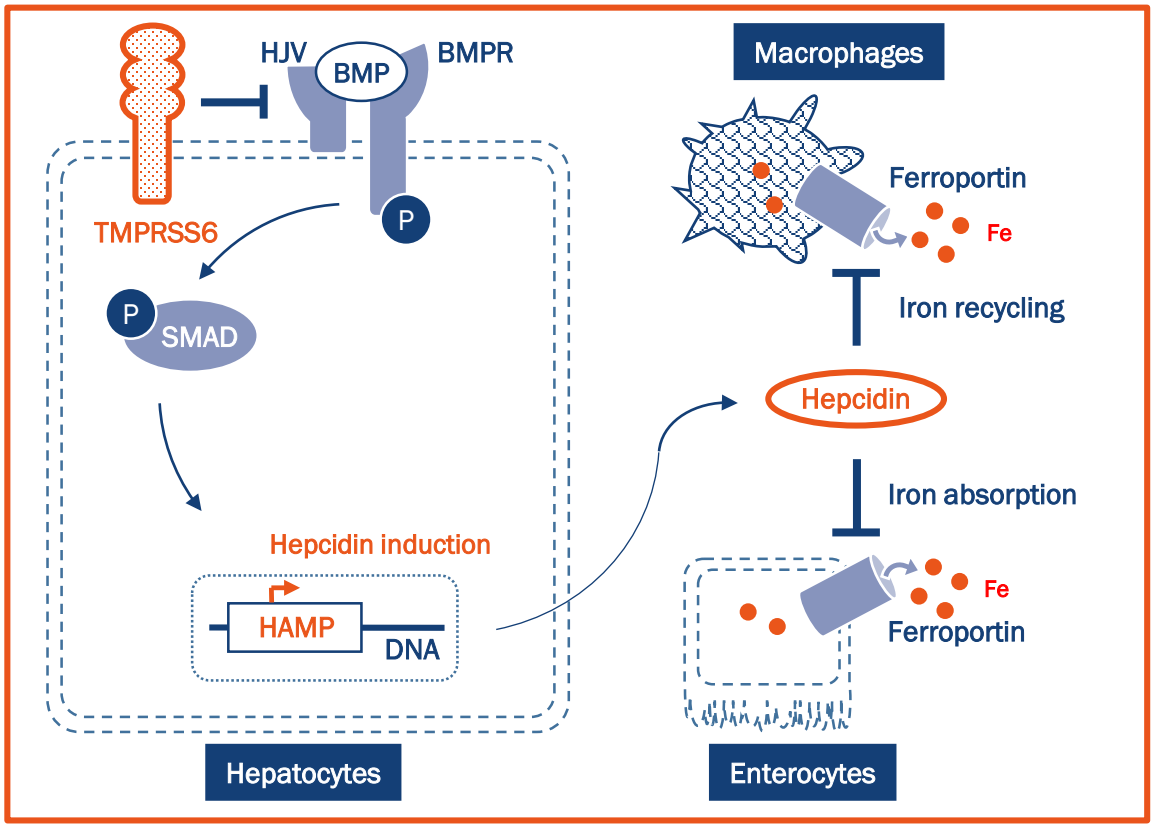
Reduced transfusion frequency &
Secondary iron overload burden

Advantages v Competition



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



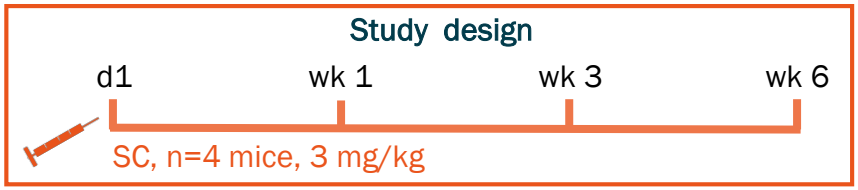
- **TMPRSS6** (Transmembrane Protease, Serine 6) is a negative regulator of the BMP/SMAD signaling pathway
- Inhibition of TMPRSS6 in hepatocytes induces Hepcidin expression
- Hepcidin reduces absorption of dietary iron and the release of iron from cellular storage, thereby reducing circulatory iron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

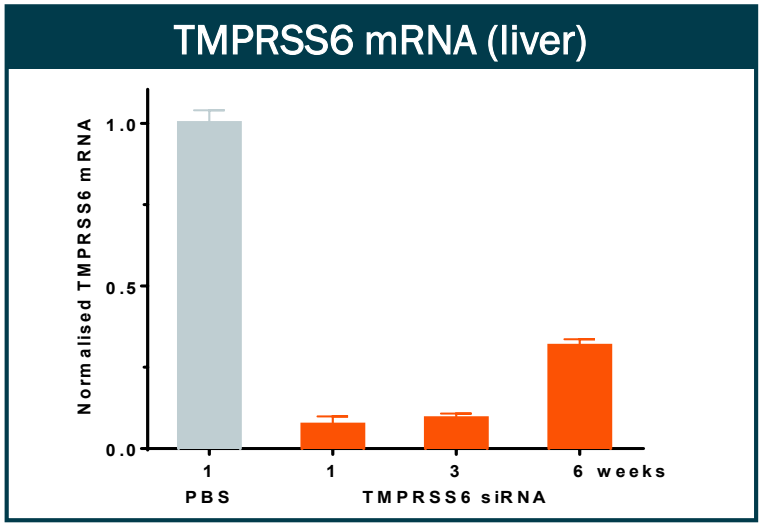
Silencing TMPRSS6

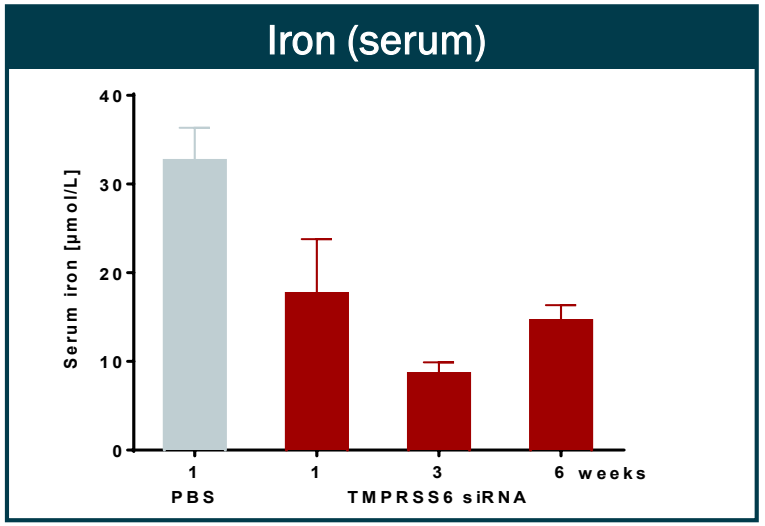
1. Increases Hepcidin levels
2. Reduces iron levels
3. Improves erythropoiesis
4. Reduces anemia & iron overload

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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

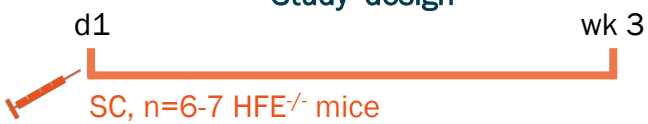
> **Well tolerated with long duration of action in mice**

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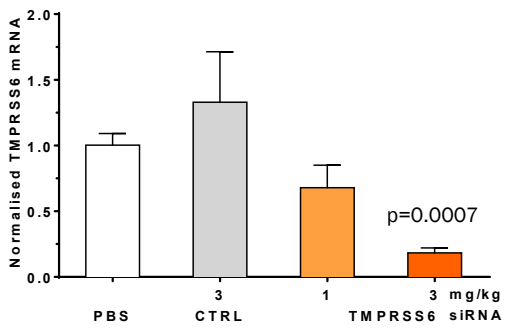
Therapeutic Activity of SLN124 in a Disease Dodel of Hereditary Haemochromatosis (HFE$^{-/-}$ mice)

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

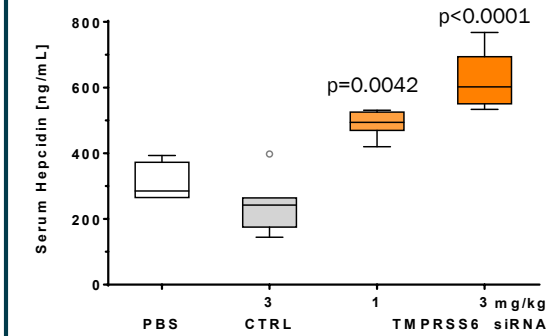
Study design



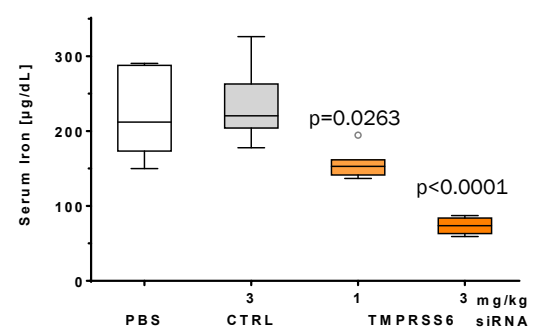
TMPRSS6 mRNA (liver)



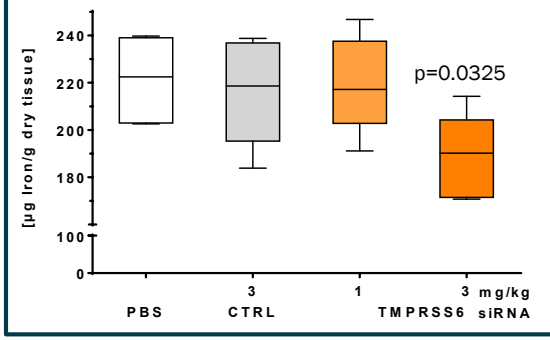
Hepcidin (serum)



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

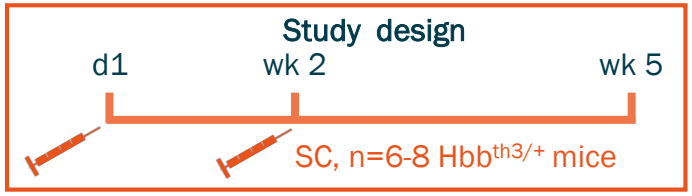
Kruskal-Wallis test with uncorrected Dunn's test against non-targeting control CTRL

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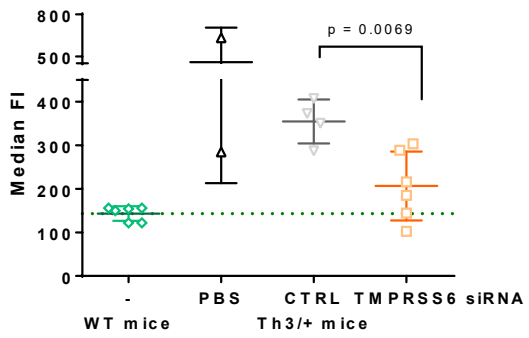
SLN124 Reduces ROS and Improves RBC Parameters in a b-Thalassemia Disease Model

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

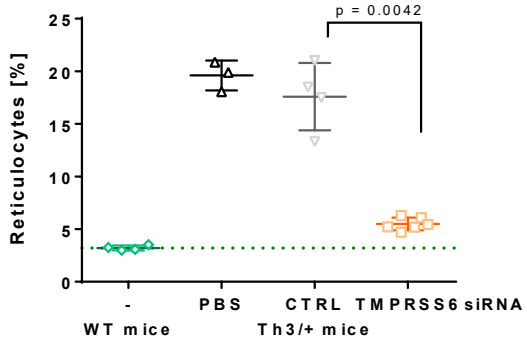
HUDSON INSTITUTE OF MEDICAL RESEARCH



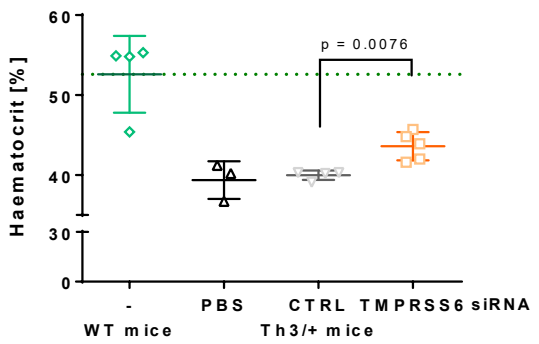
Reactive oxygen species (ROS)



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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SLN124 Summary

- **Preclinical package**: Robust data generated in several disease models
- **Status:** Non-clinical development work ongoing, with CTA filing expected in Q2 2019
- **Clinical plans:** Phase 1b planned in patients (β–Thalassaemia and MDS). Network of KOL's established
- **Dosing regime:** Patient-friendly, with a monthly or less frequent schedule envisaged and subcutaneous administration route
- **Regulatory**: after submitting the SLN124 Briefing Document to the UK Medicines and Healthcare products Regulatory Agency, positive feedback was received at the June Scientific Advice Meeting
- SLN124 is **commercially viable** compared to gene therapy, which has a heavy burden on patients versus a monthly SubQ.

SLN124 is well positioned to offer a potentially safe and potent disease-modifying treatment option to patients living with iron overload disorders, such as β–Thalassaemia (both TDT and NTDT patients)

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Expected Newsflow & Company Milestones

	Q4 2018	H1 2019	H2 2019
SLN124			
CTA enabling toxicology	⊙		
File CTA		⊙	
First In Human dosing			⊙
CV disease			
pPoC in NHP	⊙		
2018 new Targets			
POM data available	⊙		
pPOC in mice		⊙	⊙
Final candidate nomination			⊙
Alcohol Use Disorder			
CTA enabling toxicology			⊙
Platform Strengthening			
Gen3 design in use for new targets	⊙		
Gen4 toolbox validated and in use		⊙	
Quark Out-License in QP-1002			
First interpretative results for DGF Phase III study expected	⊙		
Alnylam Litigation			
UK court hearing	⊙		
Expected UK court hearing verdict		⊙	

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Thank you