SILENCE THERAPEUTICS

OPT Congress, 28 March 2018

Case Study: Identification and Development of SLN124, a Conjugated GalNAc-siRNA Therapeutic for the Treatment of Iron Overload Disorders

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Forward looking statements

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About Silence

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About Silence Therapeutics

Only quoted European RNA interference player

Key Performance Indicators:

> Net cash position of £43M at 2nd of Jan 2018

> Market cap: £136.5M*

> EV: ~ £104M*

Headcount:

> 42 FTE (27 in Berlin, R&D and 15 London, Corporate and R&D)

Listing:

> AIM, London Stock Exchange

Our facilities

HQ in London



R&D in Berlin



** As of 4 February 2018*

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Building a strong pipeline through the creation of a highly functional R&D organisation



Diverse technologies (CRISPR, mRNA, siRNA with LNP)

Decision to focus on GalNAc-siRNA platform

Building a GalNAc-siRNA therapeutic portfolio

Outsourcing routine work

2015 | 2016 | 2017 | 2018

Technology-driven R&D organisation

Drug Discovery team restructured

Technology Innovation group created

Experienced management team to execute strategy

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Experienced Leadership Team: Strong background in discovery and development of RNA therapies



Ali Mortazavi,
Chief Executive Officer



Torsten Hoffmann, Ph.D.
Chief Operating Officer



David Ellam,
Chief Financial Officer



Dmitry Samarsky, Ph.D.
Chief Scientific Officer



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



Michael Mulqueen,
Head of BD & Licensing



Alison Gallafent,
Head of Intellectual Property



Ulrich Zügel, Ph.D.
Head of Pre-Clinical Drug Discovery



Linnea Elrington,
Head of Human Resources

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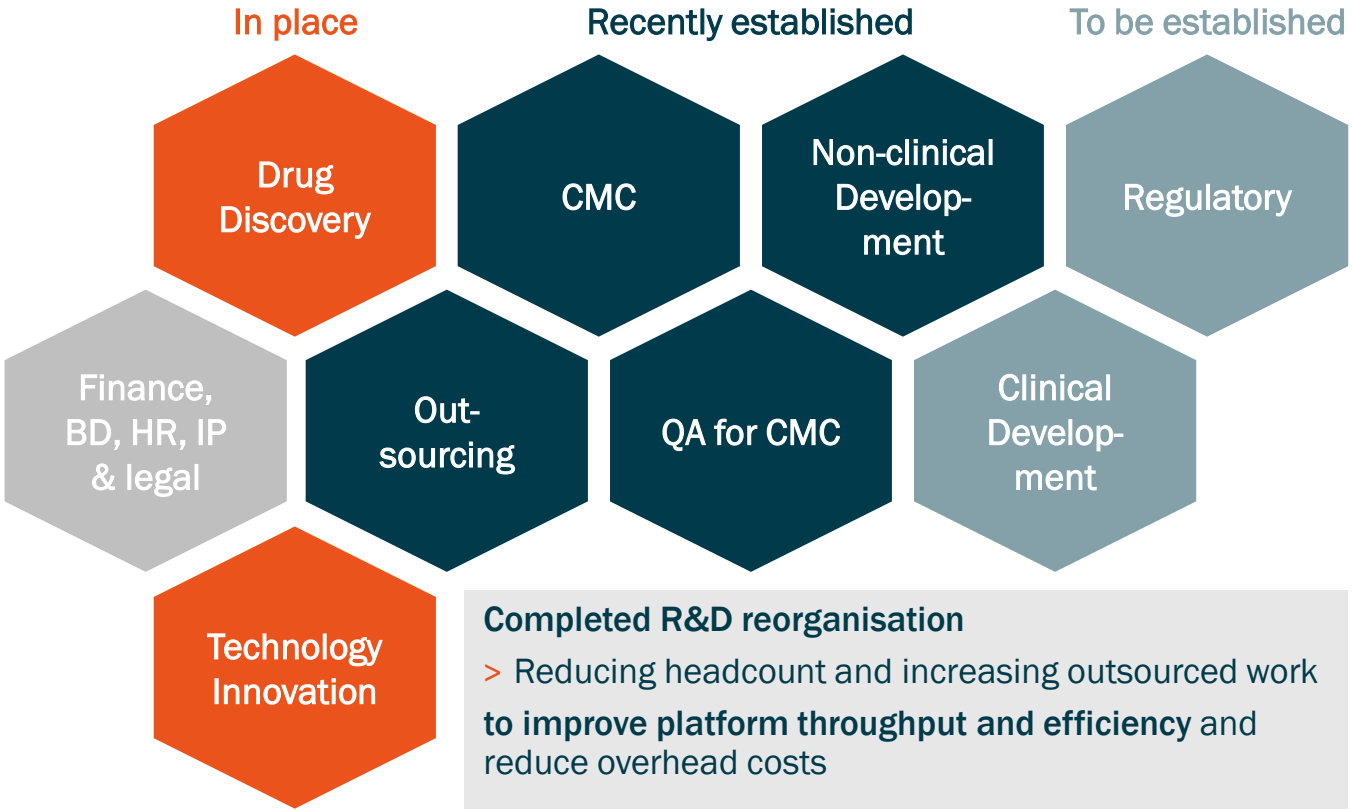
Evolving modular R&D capabilities



Completed R&D reorganisation

> Reducing headcount and increasing outsourced work

to improve platform throughput and efficiency and reduce overhead costs

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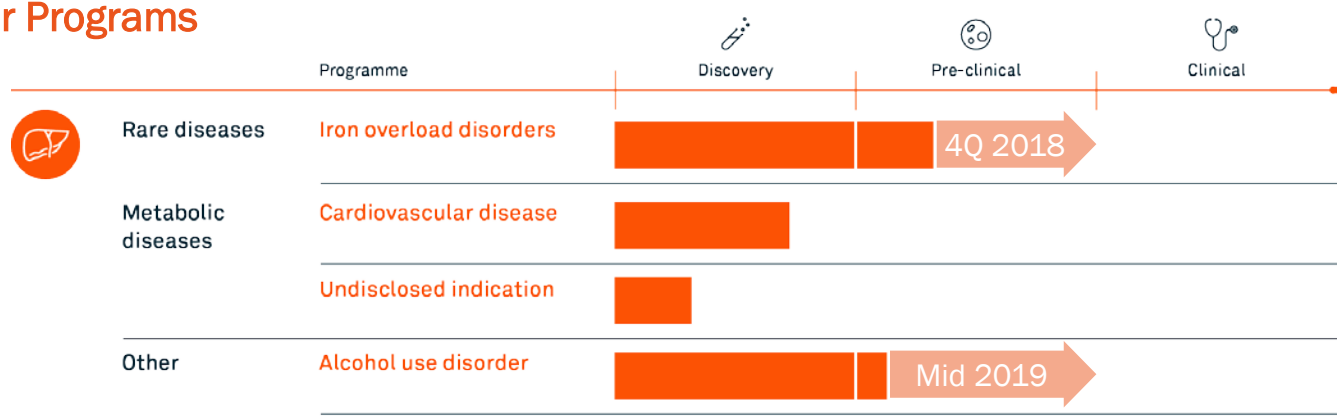
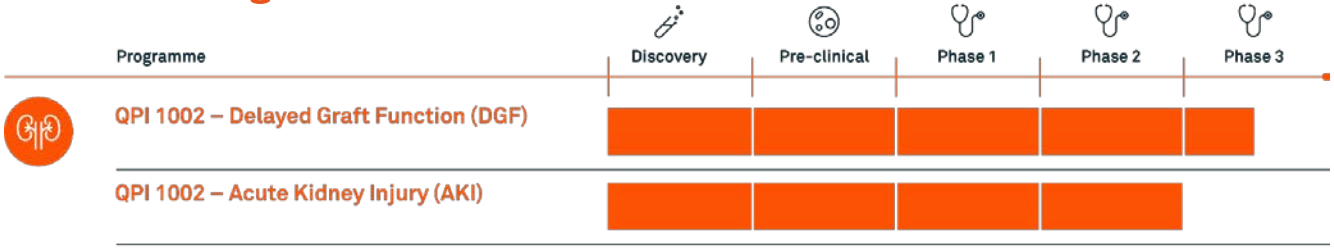
Pipeline

Building a proprietary portfolio, two projects advanced into preclinical development

Our Programs



Out-Licensed Programs



Quark

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GalNAc conjugated siRNA technology

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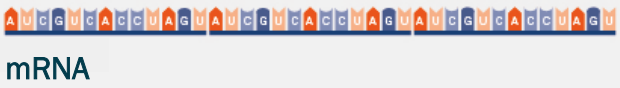
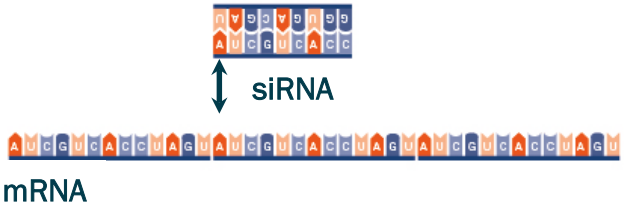
siRNA mechanism of action

1. mRNA sequence for target gene X



2. siRNA designed specifically against target gene X



3. Antisense strand binds to mRNA complementarily



4. mRNA degradation and gene silencing



RNA interference is

> A Nobel prize-winning discovery

> A natural pathway that can be harnessed to inhibit the expression of disease-causing genes without altering DNA

We can specifically target any gene in the genome with our short interfering RNA (siRNA) molecules

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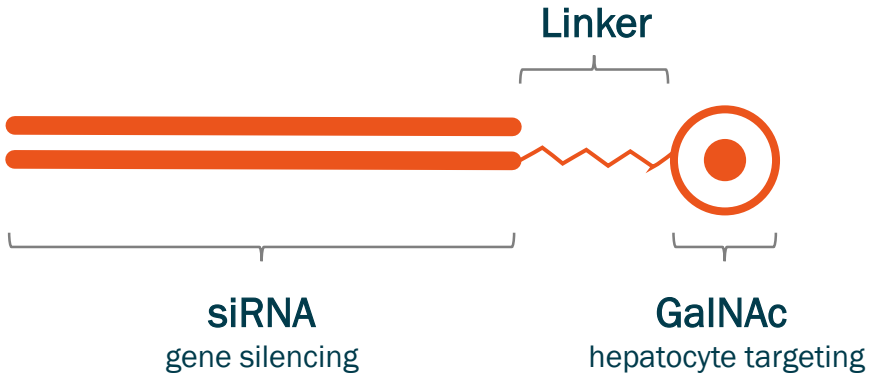
GalNAc-siRNA molecules



Advantages of GalNAc-siRNA technology

> GalNAc targets therapeutic siRNA molecules **specifically to hepatocytes**

> Highly specific by targeting a **single gene**

> Patient-friendly via **infrequent subcutaneous administration**

> Established **clinically validated technology**

> Generally **well tolerated**, high therapeutic index

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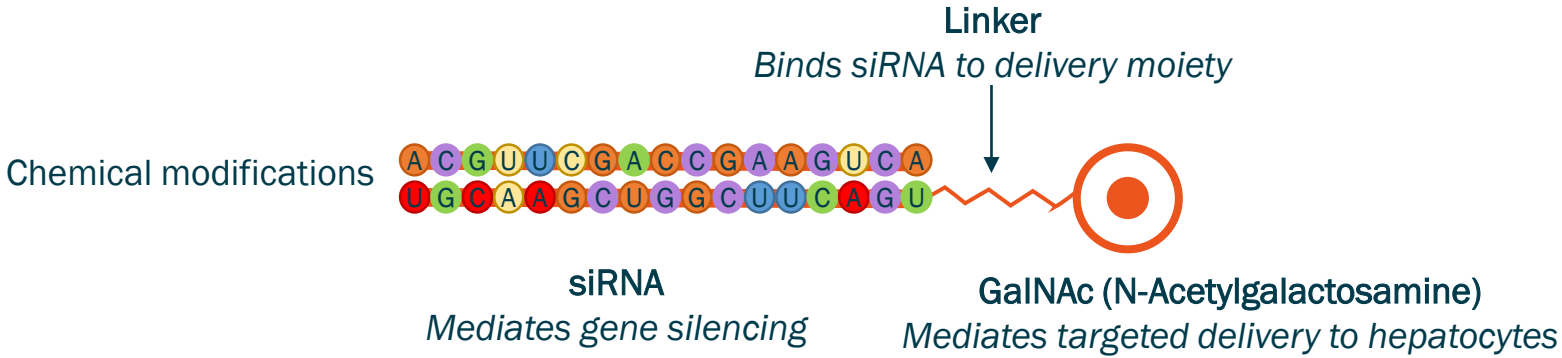
GalNAc-siRNA medicines

Schematic structure of our therapeutic molecules:



How do we ensure that our medicines are protected and free to use?

> GalNAc as a targeting ligand per se is free to use

> We have a robust position for our foundational chemical modification technology

> We patent our linker chemistries

> We patent our potent and highly specific siRNA constructs and lead sequences

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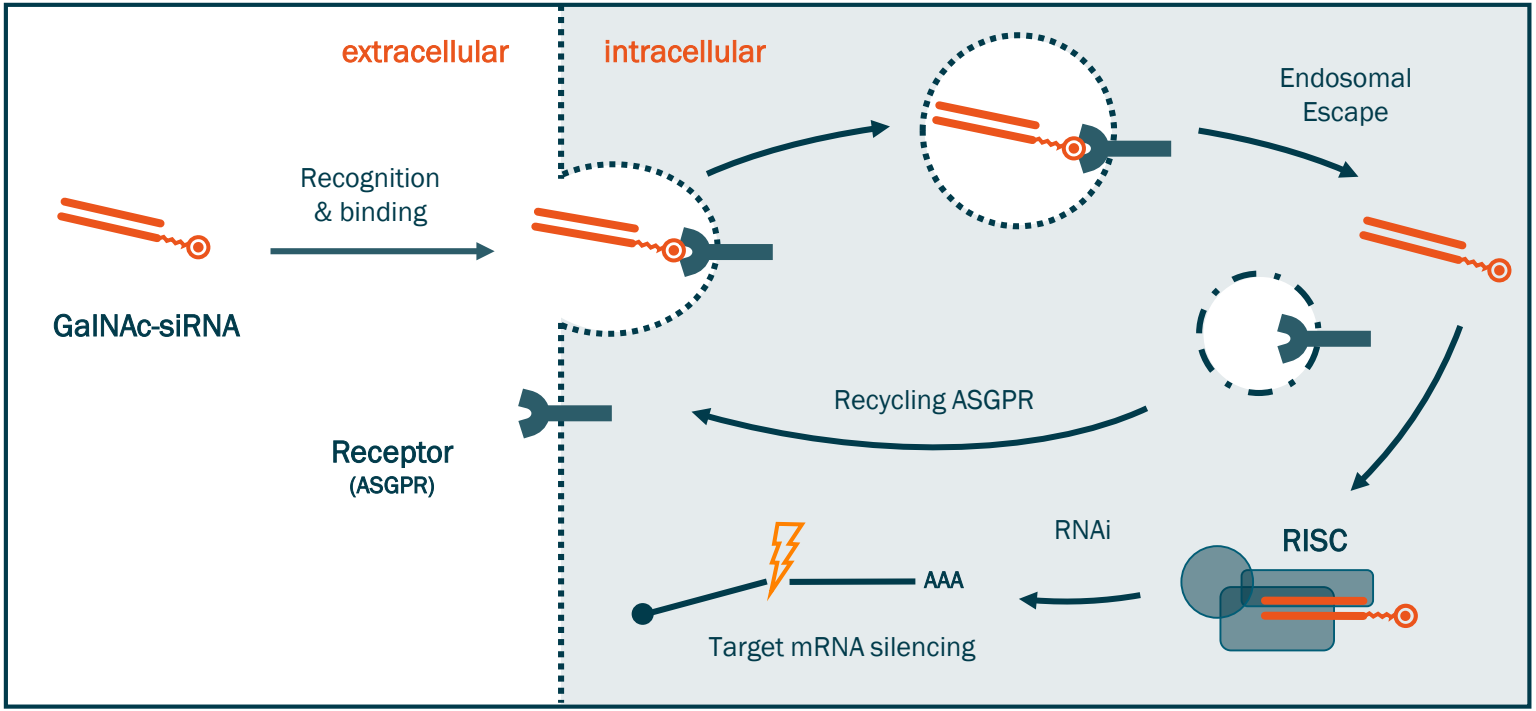
Gene silencing with GalNAc-siRNAs in hepatocytes



> Intracellular delivery mediated through receptor endocytosis

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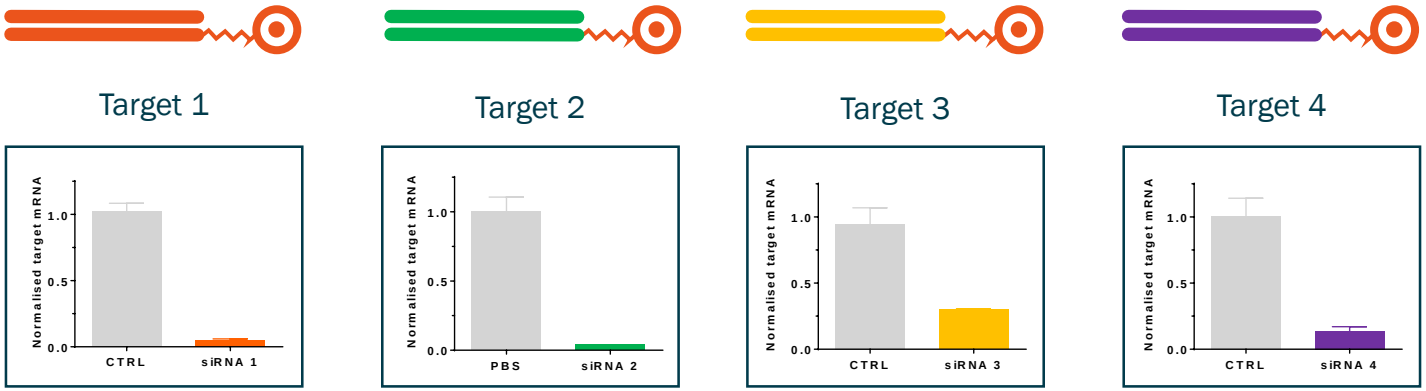
Platform performance

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

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



We are able to reproducibly silence disease-causing genes using our platform technology

Single SC dose of 2-3 mg/kg in healthy mice; analysis after 1-2 weeks

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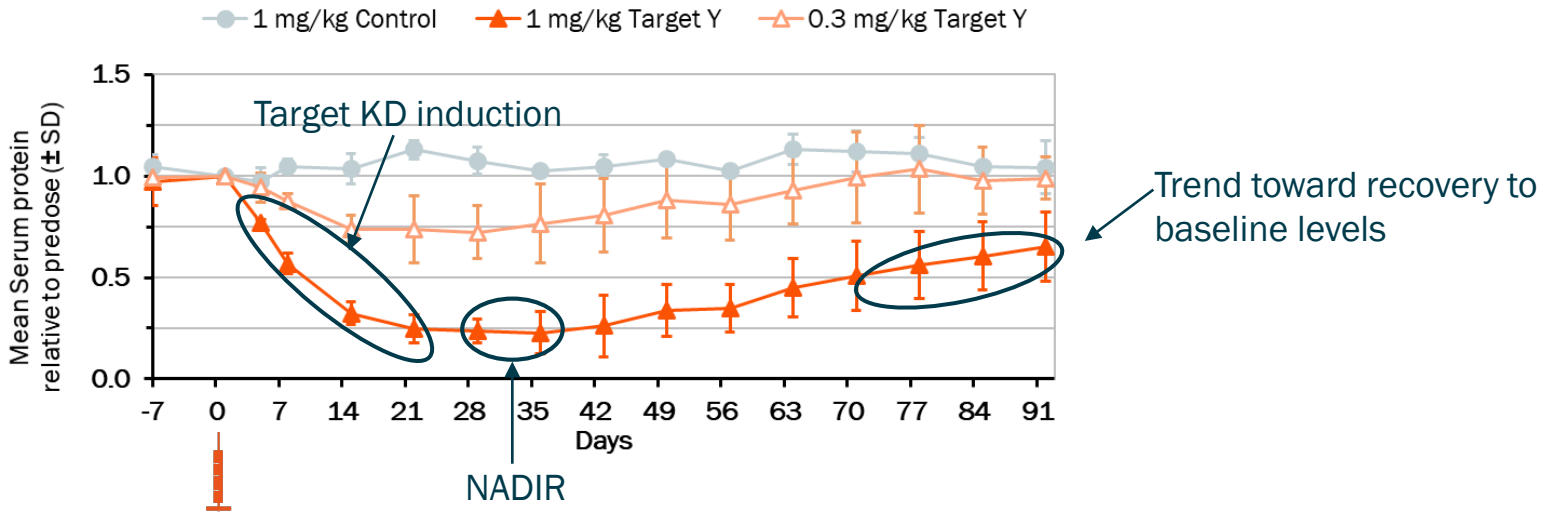
Advantageous properties of our medicines

- Subcutaneous administration, patient friendly
- Long duration of action (variable depending on target gene)
- Well tolerated
- Our GalNAc-siRNA medicines are suitable for a wide range of indications



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SLN124 for the treatment of iron overload disorders

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Treatment of iron overload disorders

GOAL

> Provide an effective and safe novel treatment option for patients with iron overload conditions, such as β-Thalassemia

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 expressed in hepatocytes

CURRENT STAGE

> Preclinical development with plans to enter clinical development in Q4/2018

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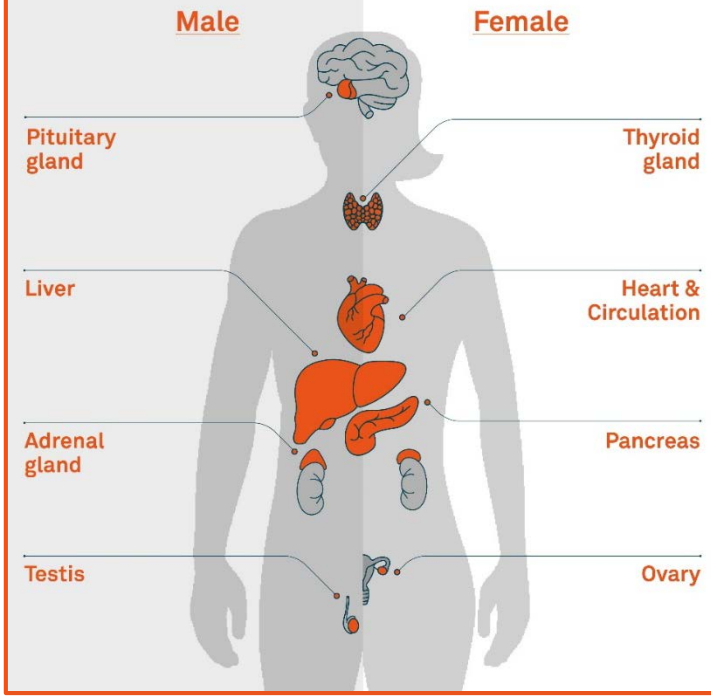
Iron Overload Disorders

Affected organs by iron overload



Diseases with iron overload

- > β-Thalassemia
- > Myelodysplastic Syndrome
- > Hereditary Haemochromatosis
- > Aplastic Anaemia
- > Sideroblastic Anaemia

If untreated, iron accumulation in organs leads to severe damage, e.g. heart, liver & endocrine organs

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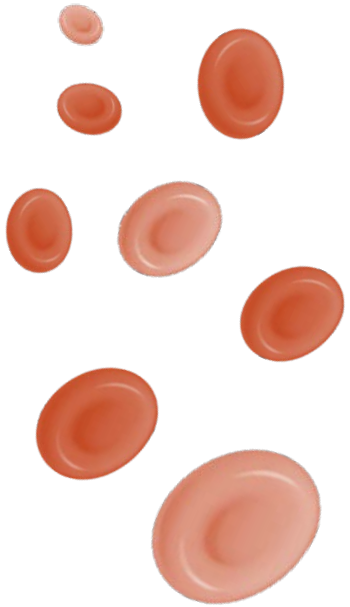
β-Thalassemia facts



- Rare blood disorder caused by mutations in the **β globin gene**
- Patients present with **ineffective erythropoiesis** and chronic **haemolytic anaemia**
- Many **β-Thalassemia intermedia** and all **β-Thalassemia major patients require transfusions to correct anaemia**
- **Ineffective erythropoiesis & blood transfusions** cause **iron overload**
- If untreated leads to severe organ damage, including **cardiac & hepatic failure** early in life

Prevalence

1/100,000 (global); 1/10,000 (Europe)

Up to 30% are genetic carriers (depending on region)



Main β-Thalassemia distribution

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Market opportunity for iron overload disorders



β-Thalassemia intermedia & T. major (TDT)

> Combination with transfusions & chelators to reduce frequency & dose

> Improve erythropoiesis and reduce secondary iron overload burden

β-Thalassemia intermedia (NTDT)

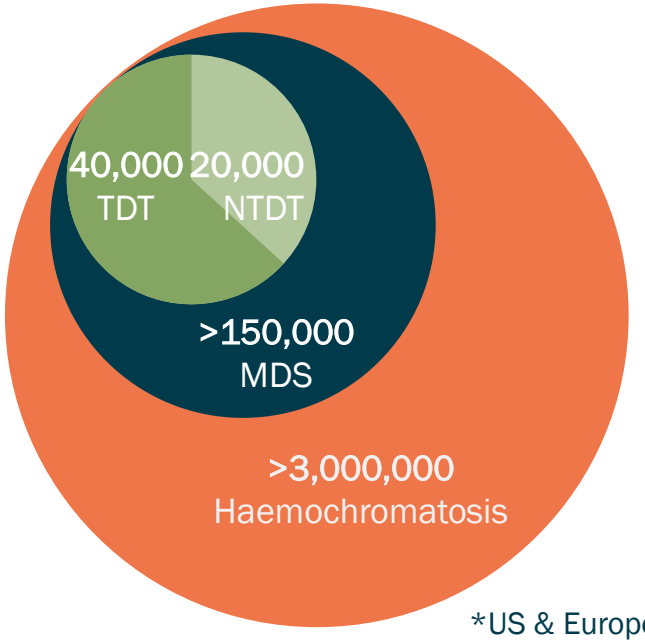
> Monotherapy to delay onset of severe symptoms

> Reduce dietary iron overload & subsequent organ damage

Other iron overload disorders

Myelodysplastic Syndrome (MDS)

Haemochromatosis



*US & Europe

SLN124 for β-Thalassemia with significant upside potential for other iron overload disorders

TDT = transfusion dependent Thalassemia; NTDT = non-transfusion dependent Thalassemia

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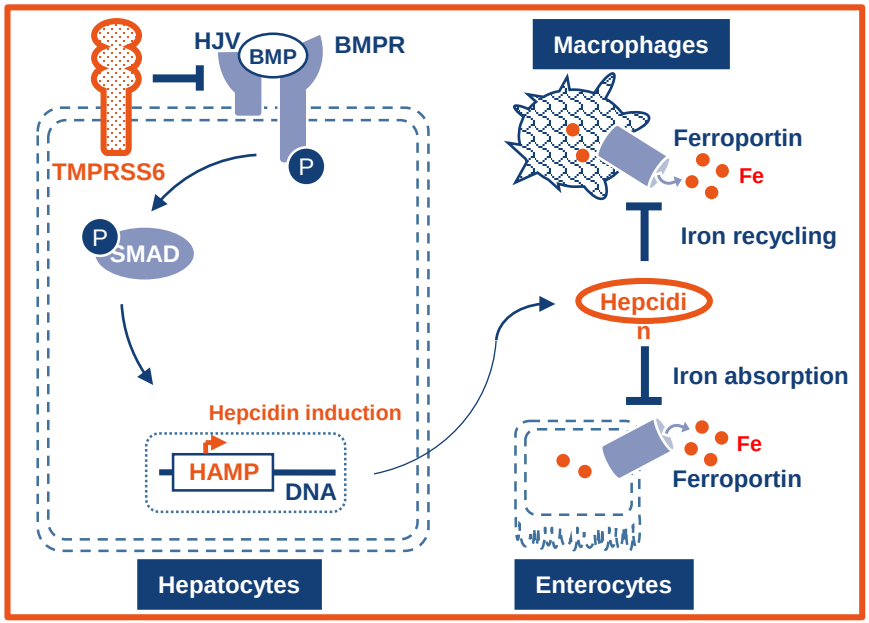
SLN124 mechanism of action



- **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 anaemia & iron overload

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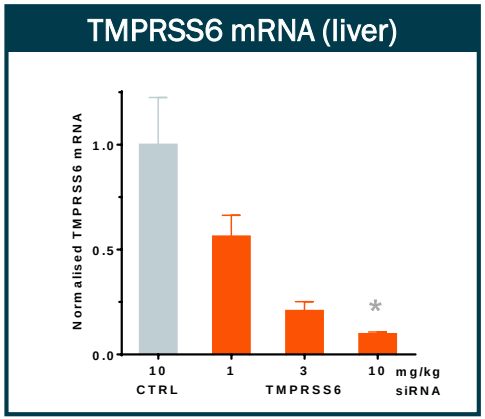
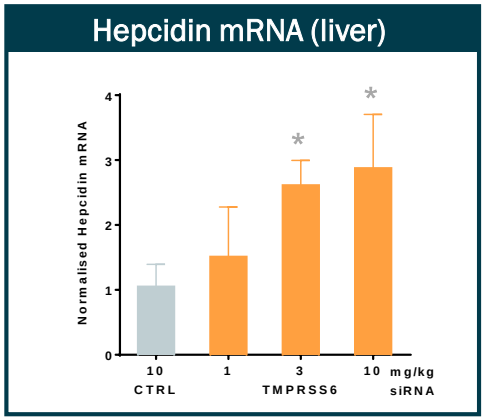
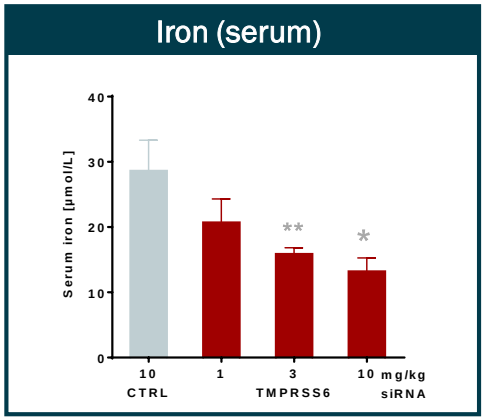
Silencing TMPRSS6 lowers serum iron levels in mice









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

> Single subcutaneous administration reduces TMPRSS6 expression

> Induction of Hepcidin causes reduction of blood iron levels

> **Proof of mechanism demonstrated**

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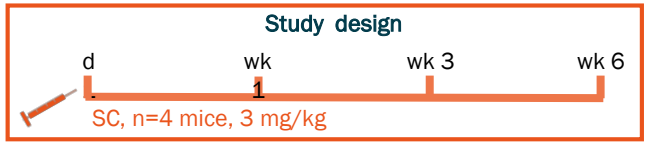
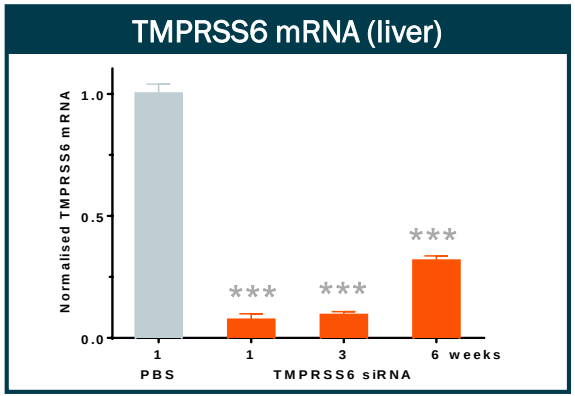
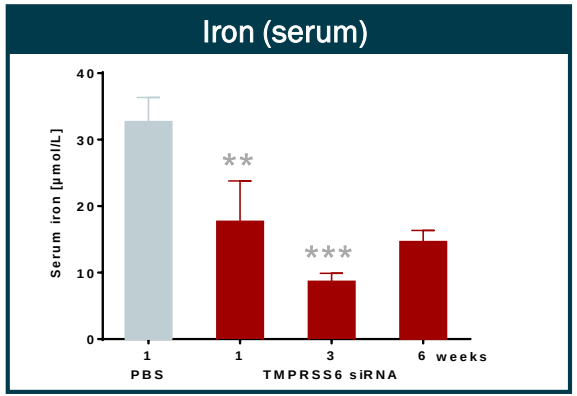
SLN124 lowers iron levels for at least 6 weeks after single administration in mice







2-way ANOVA multiple comparisons: shown to control CTRL groups (same time point)

- 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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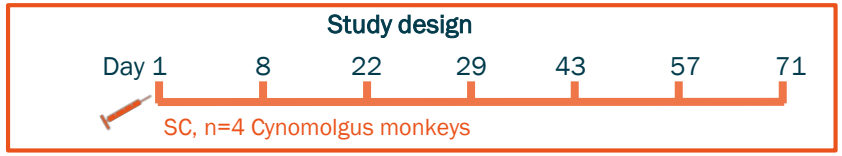
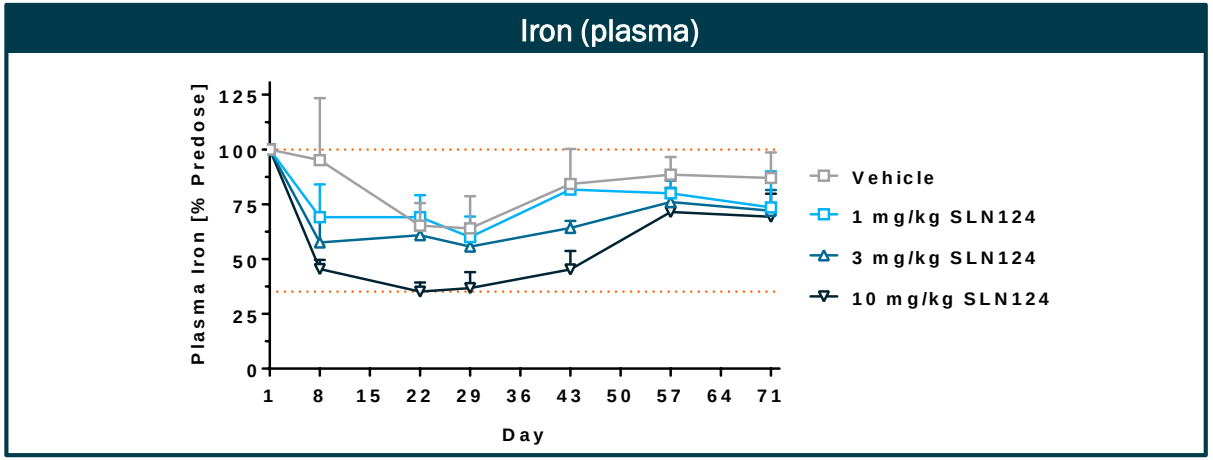
Sustained reduction of circulating iron levels after single administration in non-human primates





> Dose dependent, durable plasma iron reduction up to 6 weeks

> Well tolerated with long duration of action

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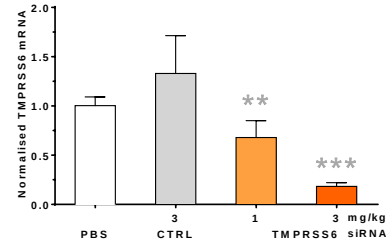
Therapeutic activity of SLN124 in a disease model for hereditary haemochromatosis ($HFE^{-/-}$ mice) - 1/2

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

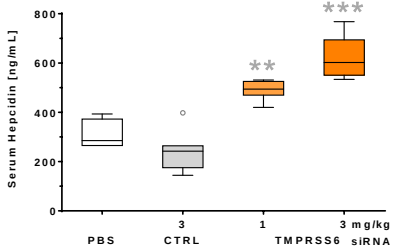
Study design



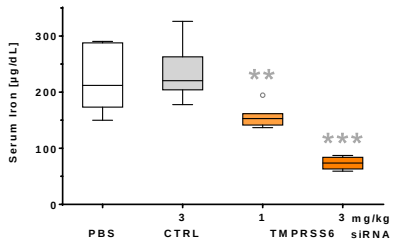
TMPRSS6 mRNA (liver)



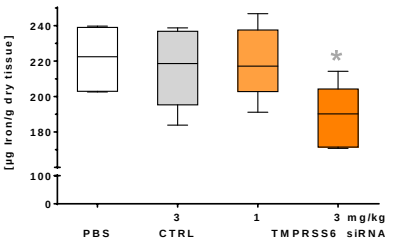
Hepcidin (serum)



Iron (serum)



Iron (kidney)



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

- 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

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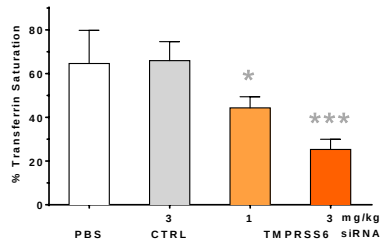
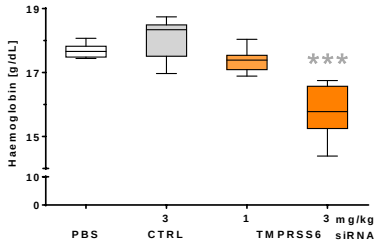
Therapeutic activity of SLN124 in a disease model for hereditary haemochromatosis ($HFE^{-/-}$ mice) - 2/2

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

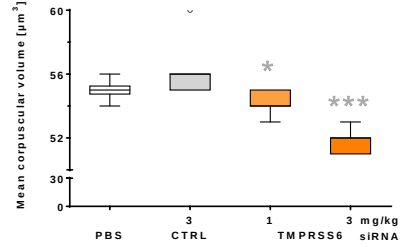
Transferrin Saturation



Haemoglobin



Mean corpuscular volume



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

> Reduction of transferrin saturation to physiological values

> Normalization of haematological parameters

> Therapeutically active in $HFE^{-/-}$ mice after single administration

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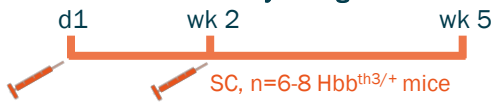
SLN124 normalizes ROS species & improves RBC parameters in β-Thalassemia disease model

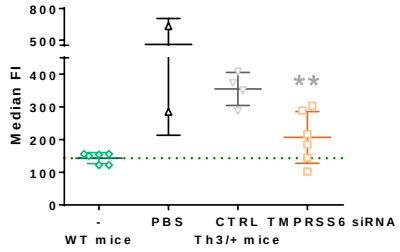
Collaboration with
Prof. J. Vadolas & Dr. Grigoriadis
Monash Medical Centre/Melbourne, Australia

HUDSON INSTITUTE OF MEDICAL RESEARCH

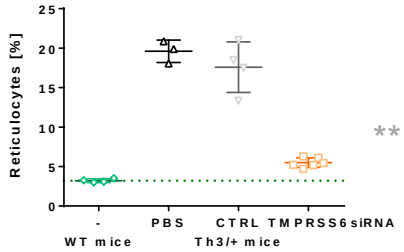
Study design



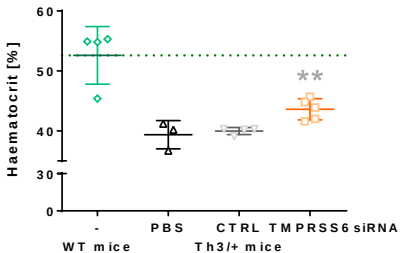
Reactive oxygen species (ROS)



Reticulocyte proportion



Haematocrit



Unpaired t test with Welch´s correction against non-targeting control CTRL

> Normalisation of ROS to levels towards values in healthy mice

> Normalisation of reticulocyte proportion and improvement of haematocrit

> SLN124 ameliorates erythropoiesis in animal model for β-Thalassemia intermedia

ROS = reactive oxygen species; RBC = red blood cells

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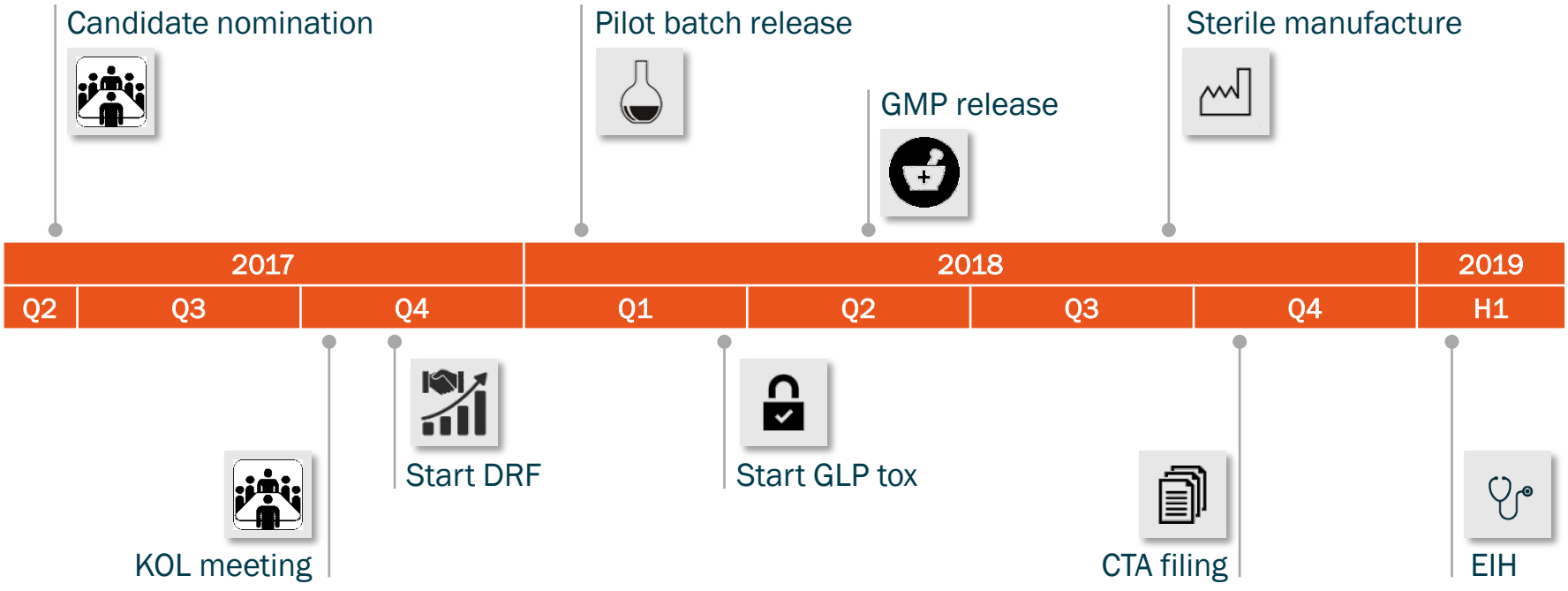
SLN124 development timelines – key milestones



On track for CTA filing 15 months after candidate selection

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SLN124 - Summary

- Highly potent, selective and long acting GalNAc-siRNA
- Efficacious in lowering blood iron and well tolerated in healthy mice and non-human primates after single subcutaneous administration
- Demonstrated therapeutic efficacy in clinically relevant animal disease models
- Currently in preclinical development with plans to enter clinical development in Q4 2018

SLN124 represents a highly valuable therapeutic candidate for patients with iron overload disorders, such as β-Thalassemia

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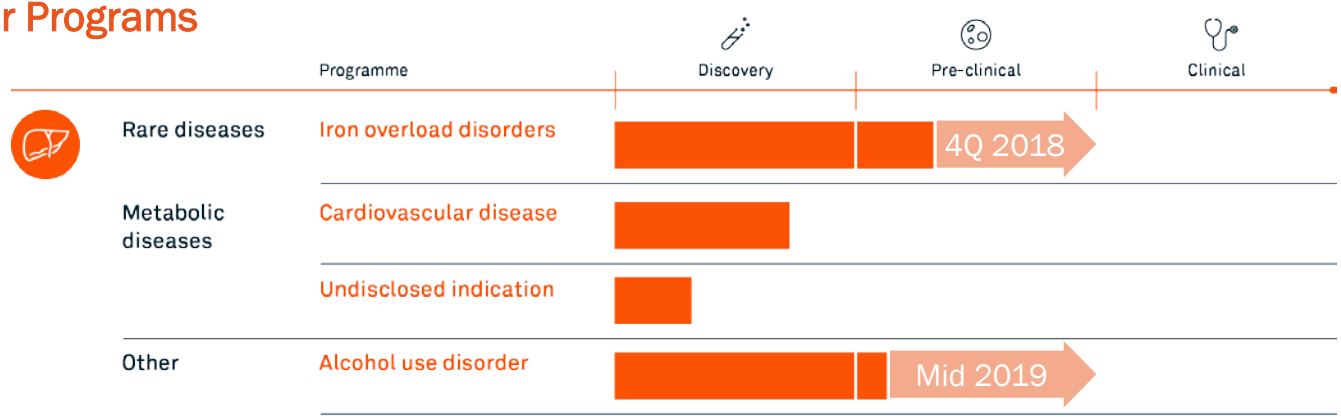
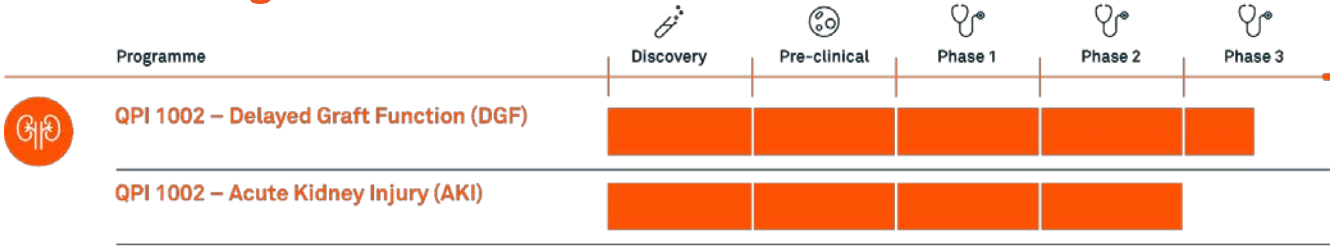
Pipeline

Building a proprietary portfolio, two projects advanced into preclinical development

Our Programs



Out-Licensed Programs



Quark

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R&D with focus on portfolio and innovation

Technology Innovation

- Improve performance of our GalNAc-siRNA molecules
- Strengthen and broaden IP portfolio
- Expand RNAi horizons beyond hepatocytes
- Apply to therapeutic portfolio upon validation



Dmitry Samarsky, Ph.D.
Chief Scientific Officer
RIBOBIO



Marie W. Lindholm, Ph.D.
Head of Technology Innovation
Roche
santaris pharma a/s

Drug Discovery & Development

- Build a proprietary therapeutic portfolio by applying validated siRNA technologies
- Partner programs in a strategic manner
- Add new programs in a risk-diversified manner



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