SILENCE THERAPEUTICS

AsiaTIDES, 1 March 2018

Use of Advanced siRNAs Targeted to Hepatocytes

for the Development of Novel Drugs to Treat Liver-related Disorders

Torsten Hoffmann, PhD
Chief Operating Officer

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

the evolution group plc | LCL Le Crédit Lyonnais



Torsten Hoffmann, Ph.D.
Chief Operating Officer

ZEALAND PHARMA | proteros | Roche



David Ellam,
Chief Financial Officer

BIOMARIN | Ark therapeutics



Dmitry Samarsky, Ph.D.
Chief Scientific Officer

RIBOBIO



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

Imperial College London | UCL



Michael Mulqueen,
Head of BD & Licensing

BIOTIE THERAPIES | Roche



Alison Gallafent,
Head of Intellectual Property

CMS Law.Tax | gsk



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

BAYER | SCHERING making medicine work



Linnea Elrington,
Head of Human Resources

GLORY | cisiv

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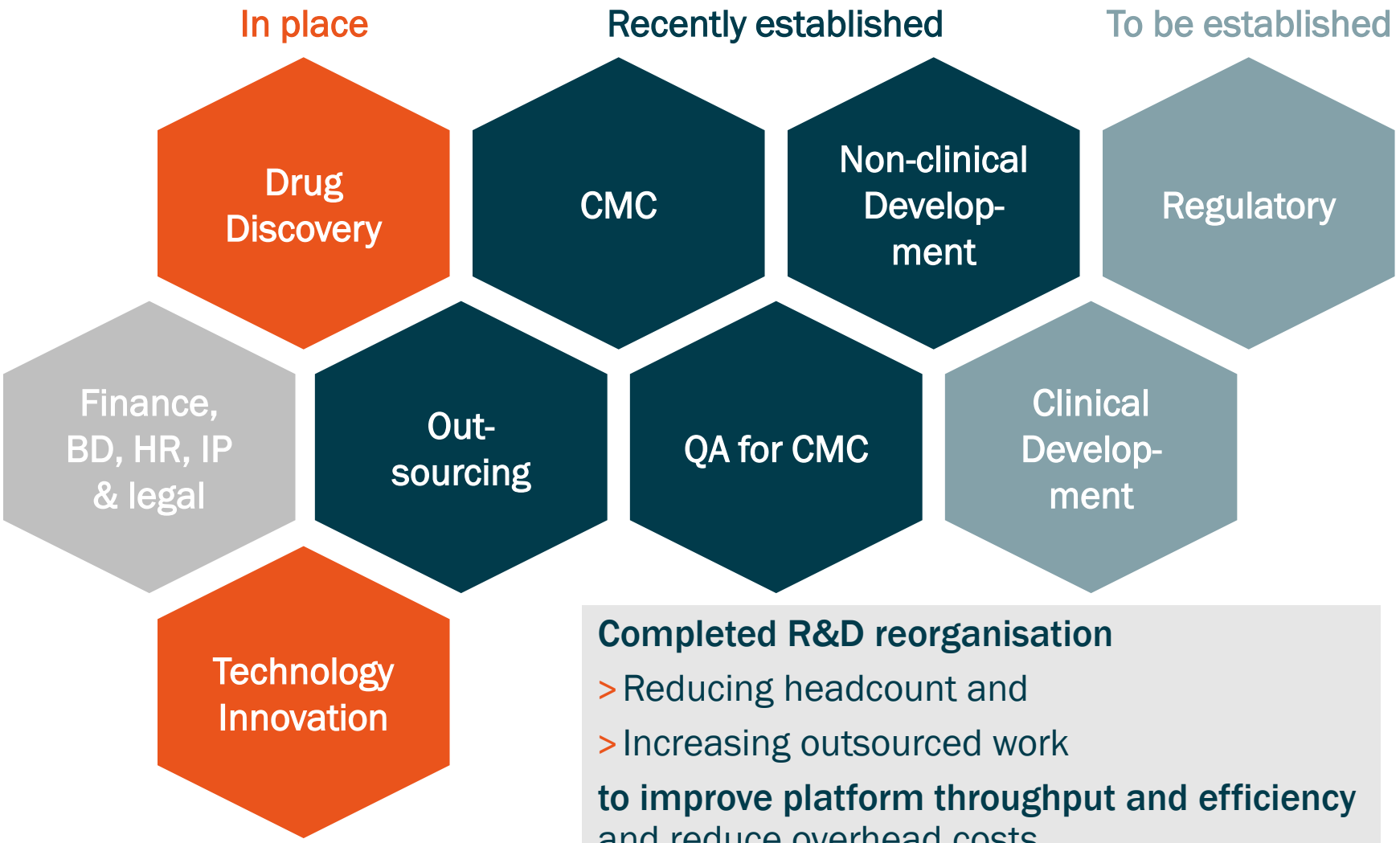
Evolving modular R&D capabilities



Completed R&D reorganisation

> Reducing headcount and

> Increasing outsourced work

to improve platform throughput and efficiency and reduce overhead costs

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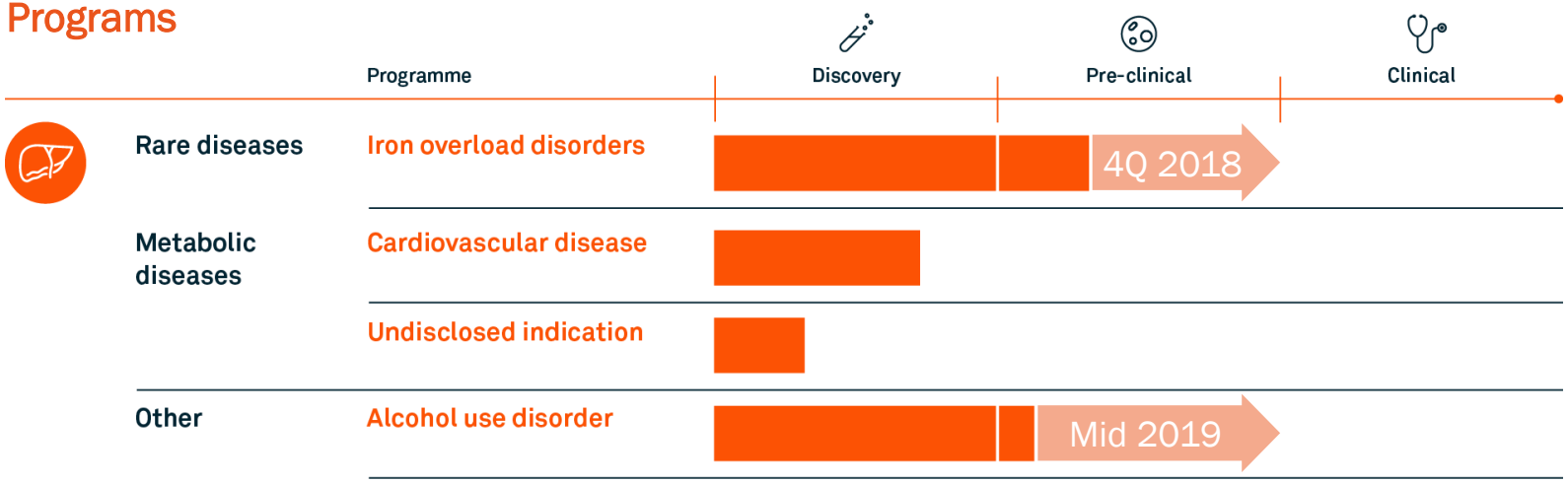
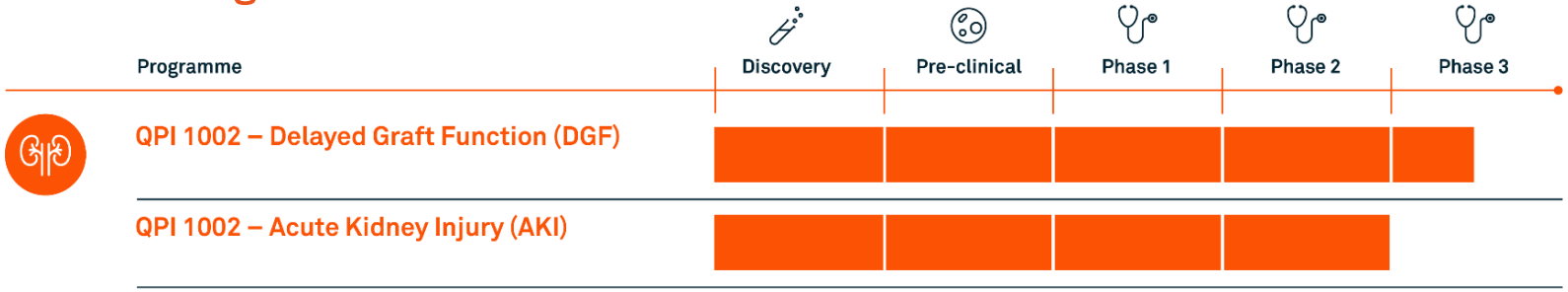
Pipeline

Building a proprietary portfolio, two projects advanced into preclinical development

Our Programs



Out-Licensed Programs



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GalNAc conjugated siRNA technology

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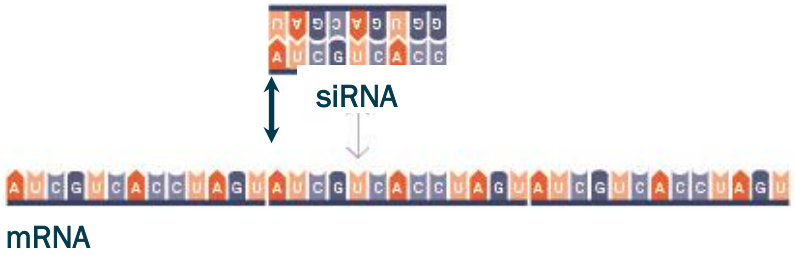
siRNA mechanism of action

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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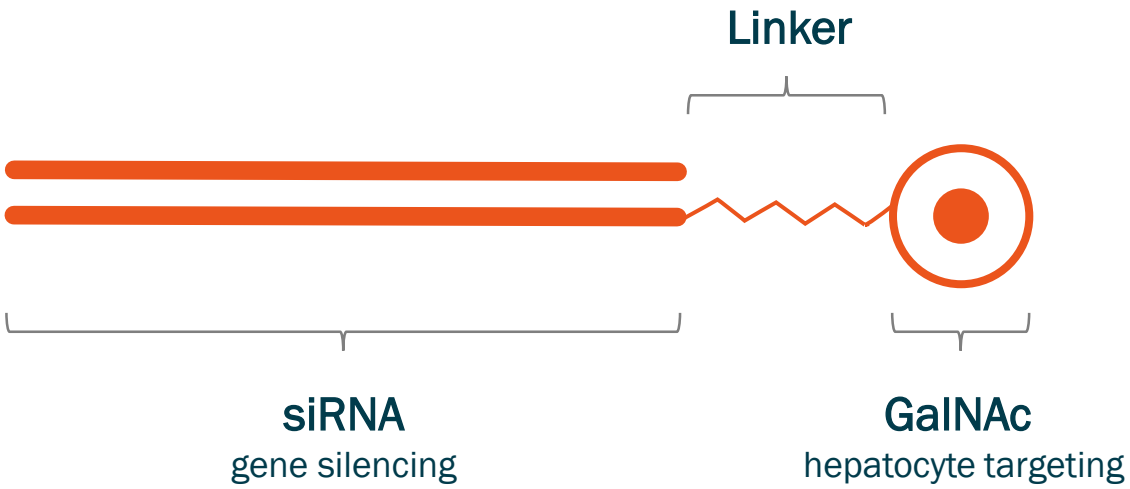
GalNAc-siRNA molecules



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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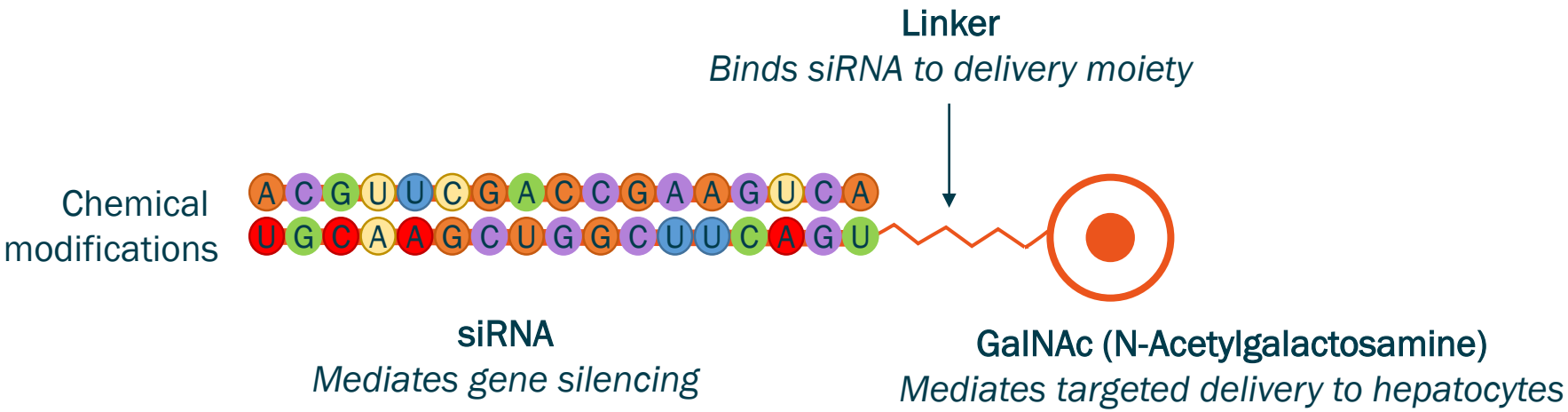
GalNAc-siRNA medicines

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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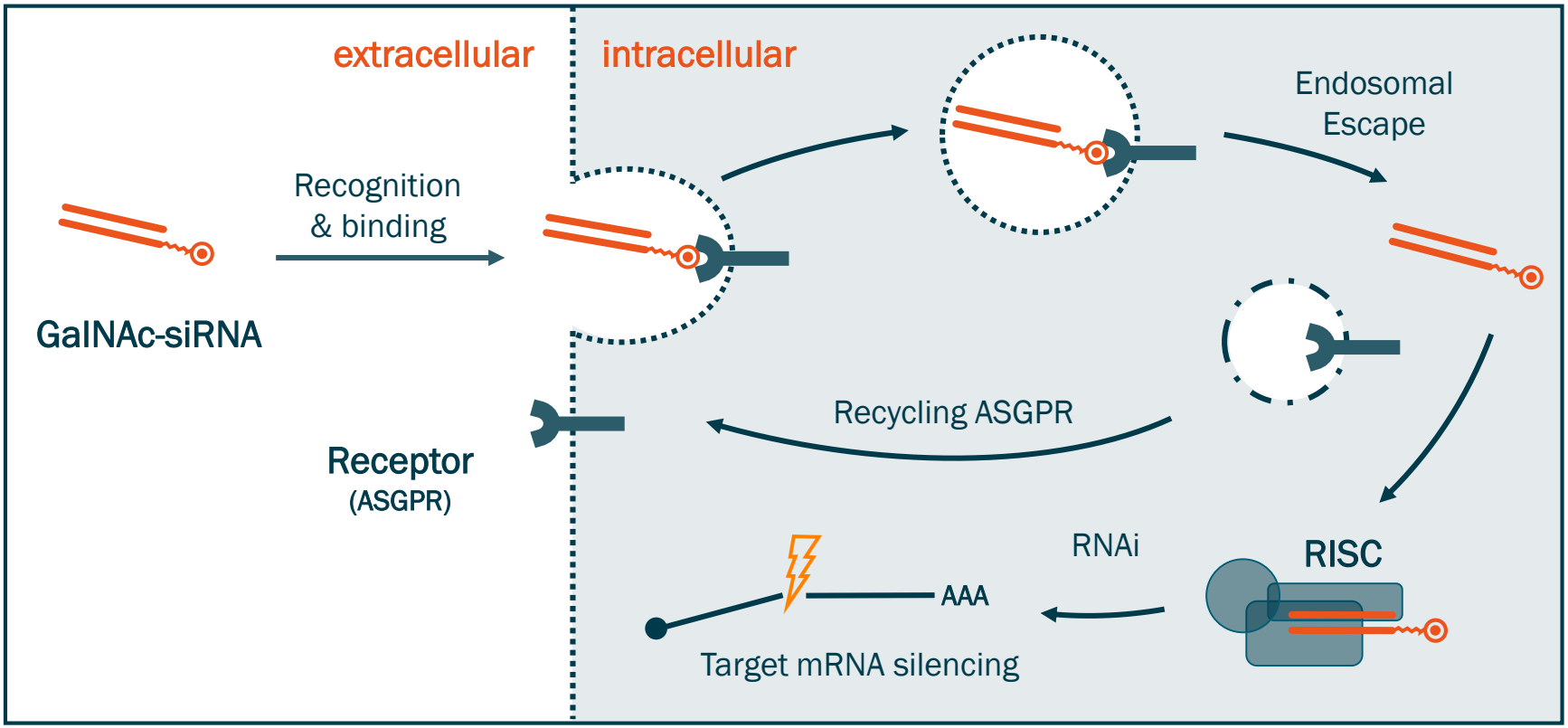
Gene silencing with GalNAc-siRNAs in hepatocytes



> Intracellular delivery mediated through receptor endocytosis

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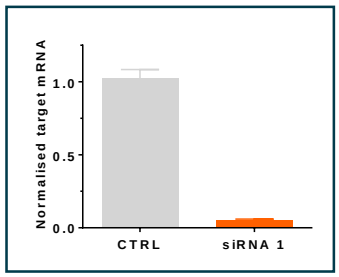
Platform performance

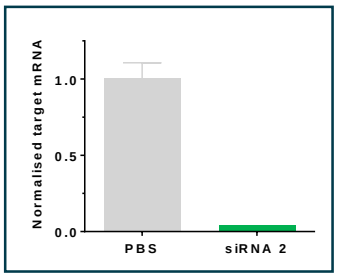
Platform technology: GalNAc-siRNA, able to mediate highly specific gene silencing in hepatocytes (liver) – "Specificity upon specificity"

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

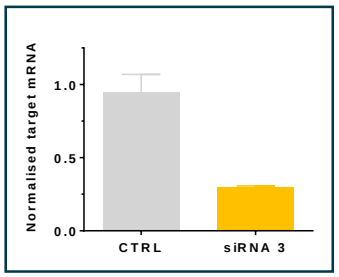
Target 1



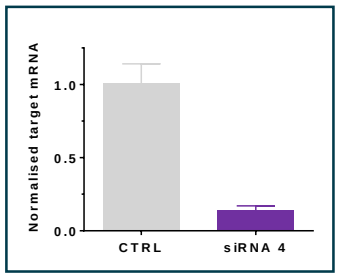
Target 2



Target 3



Target 4



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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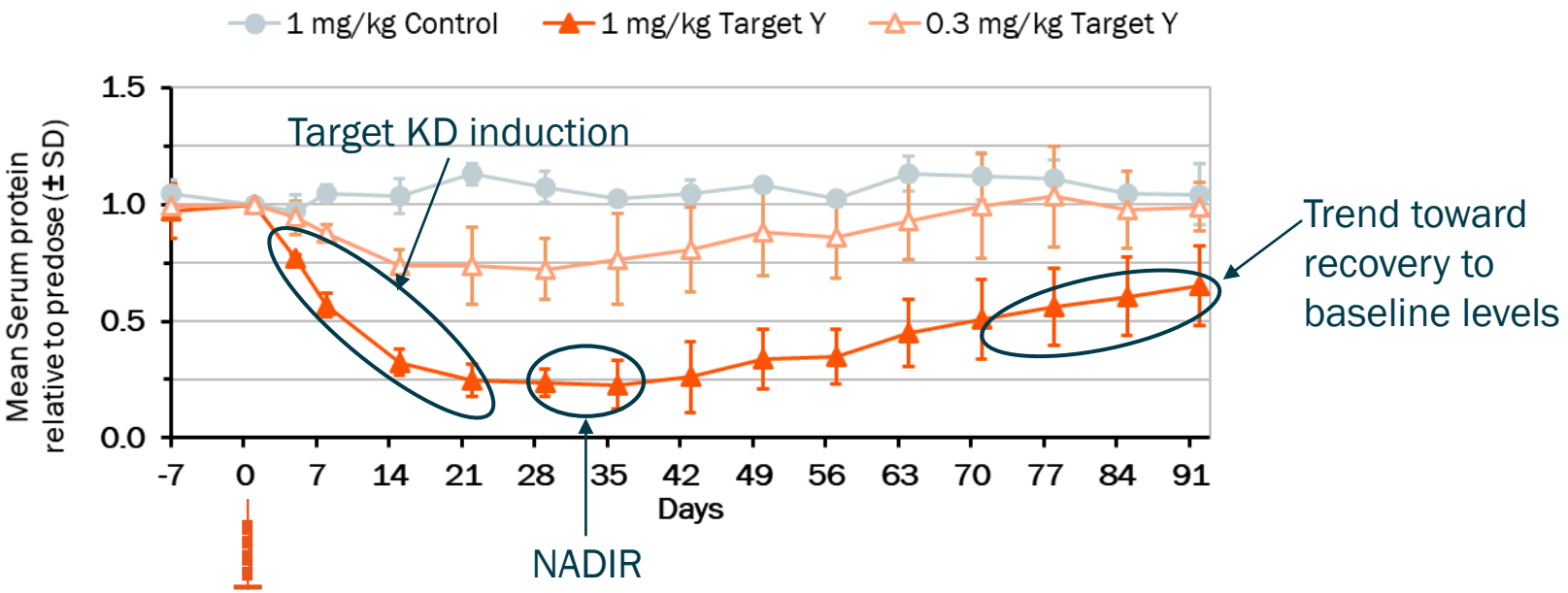
Advantageous properties of our medicines

> 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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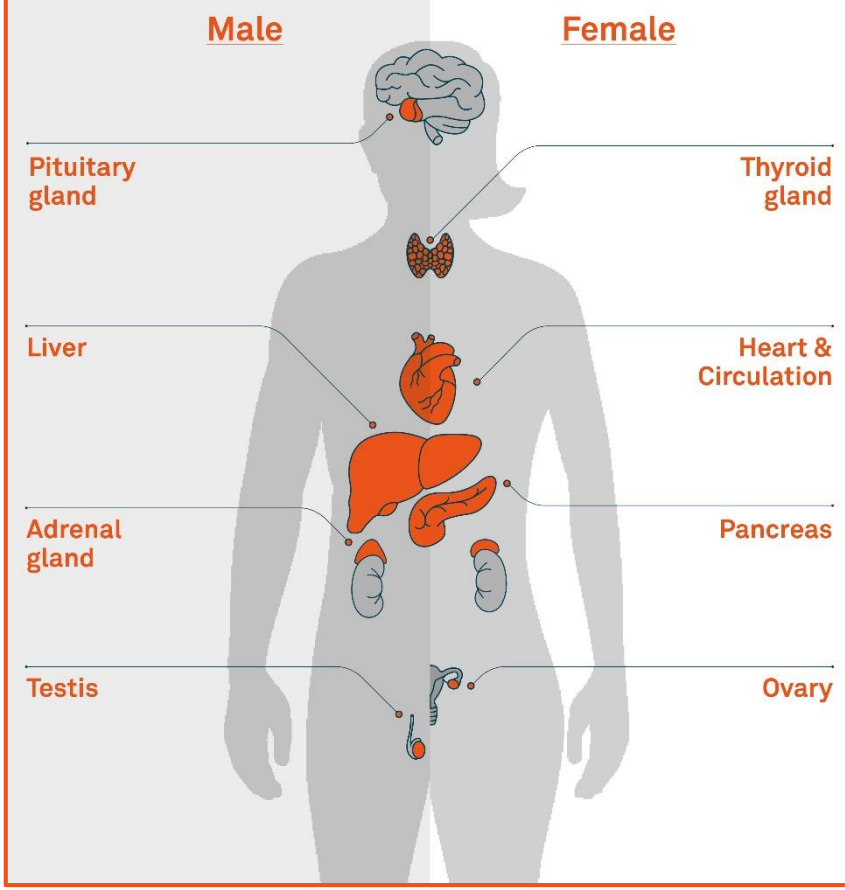
Iron Overload Disorders

Affected organs by iron overload



Diseases with iron overload

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

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

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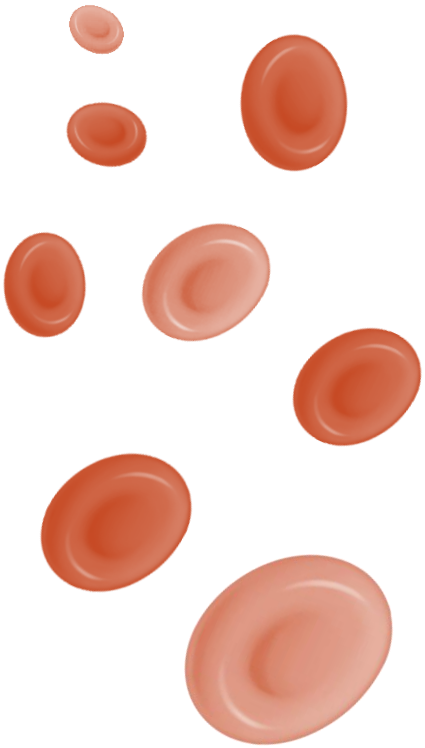
β-Thalassemia facts



- 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

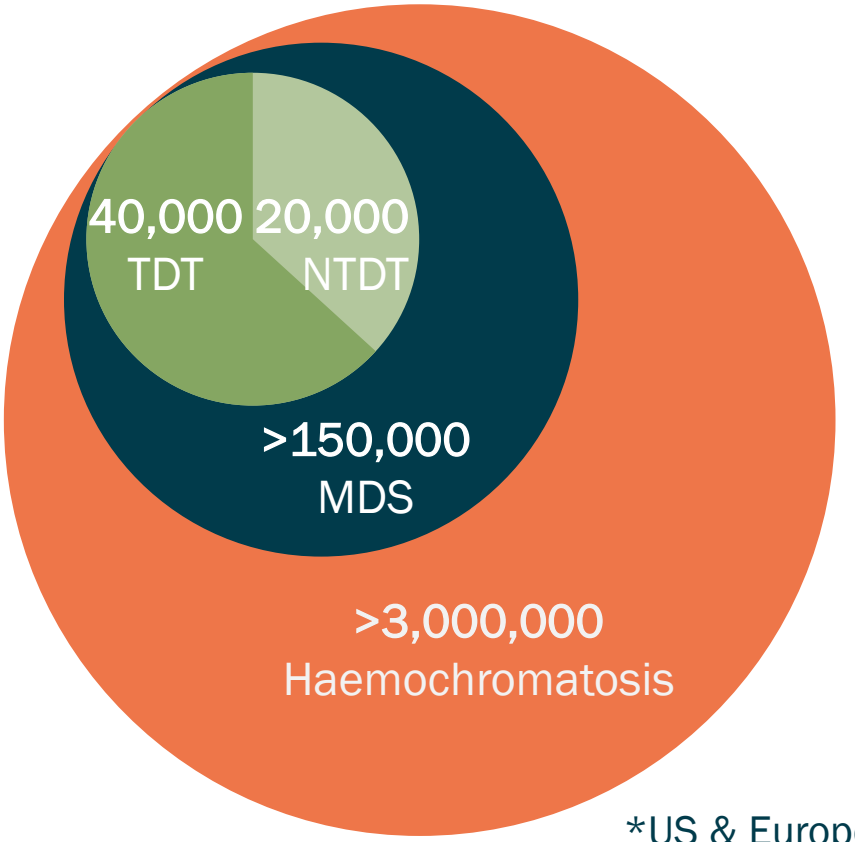
β-Thalassemia intermedia (NTDT)

- 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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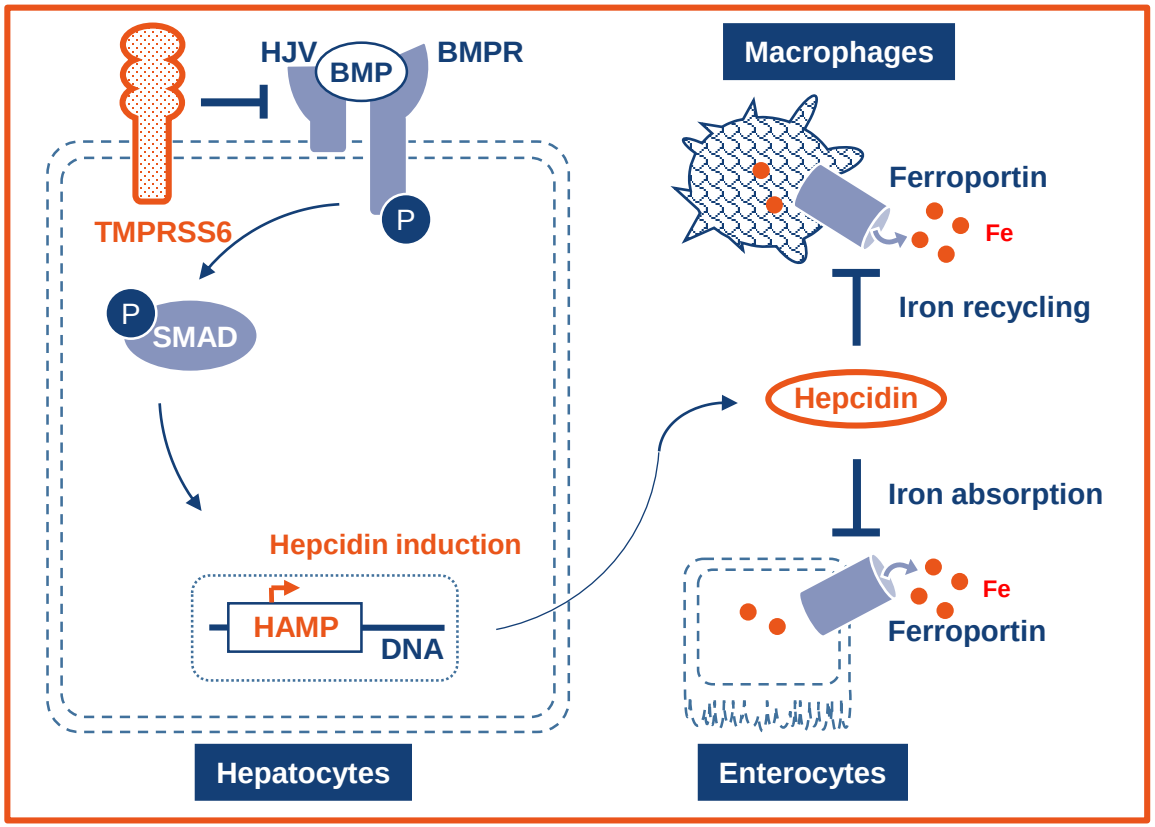
SLN124 mechanism of action



- **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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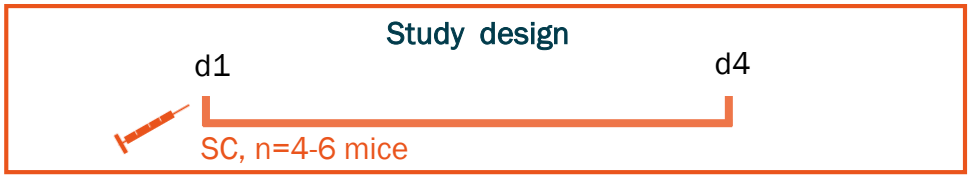
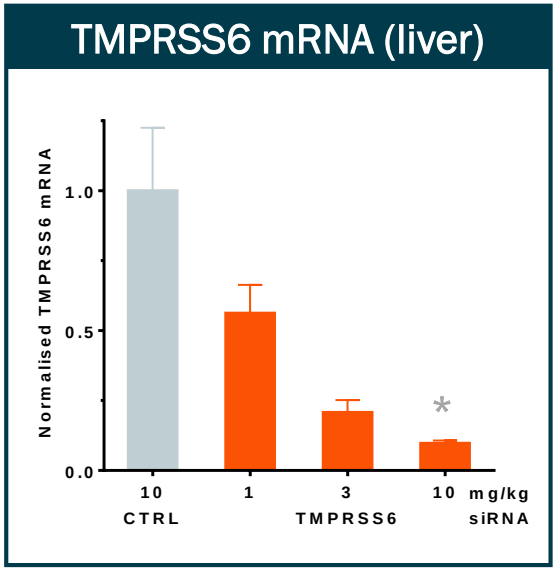
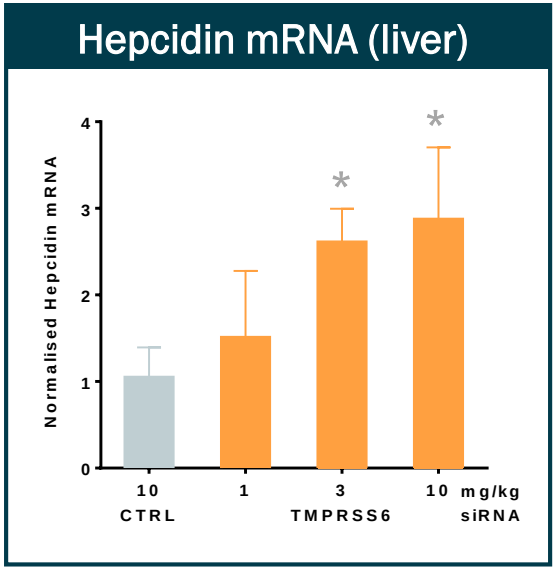
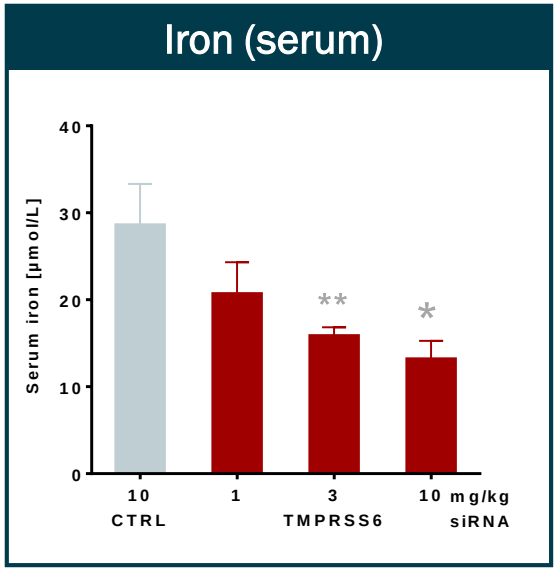
Silencing TMPRSS6 lowers serum iron levels in mice









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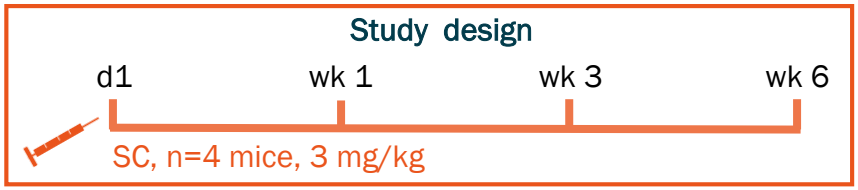
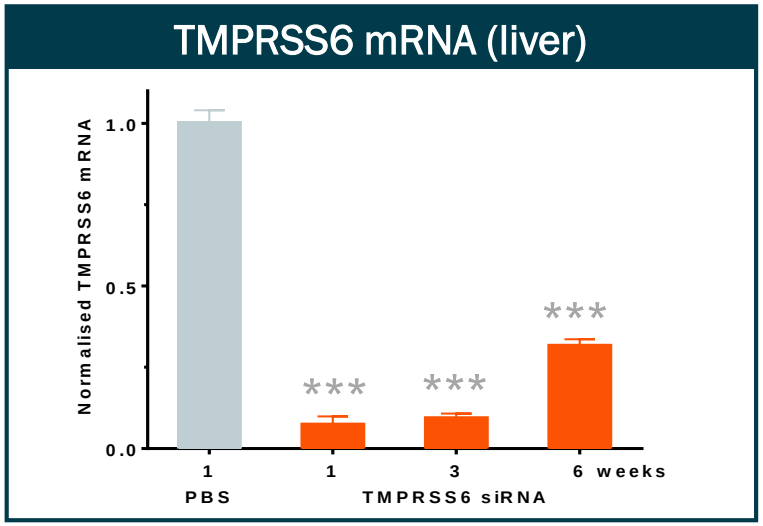
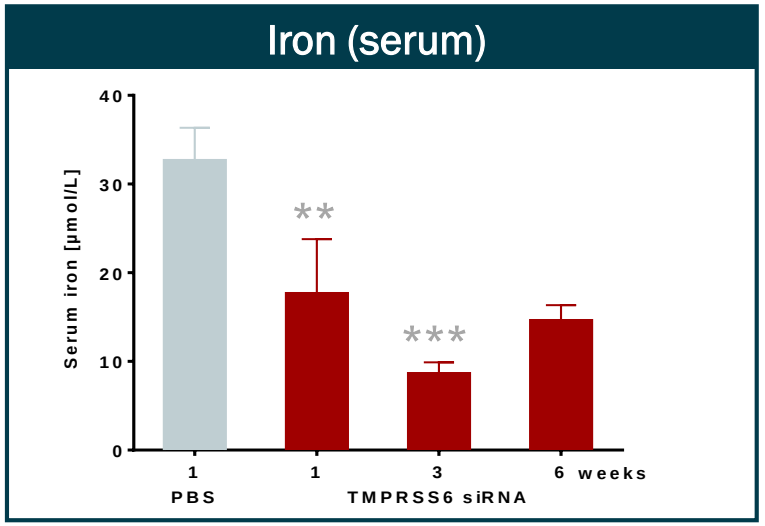
SLN124 lowers iron levels for at least 6 weeks after single administration in mice







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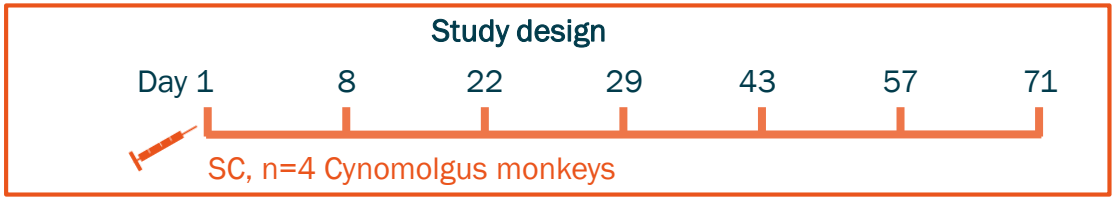
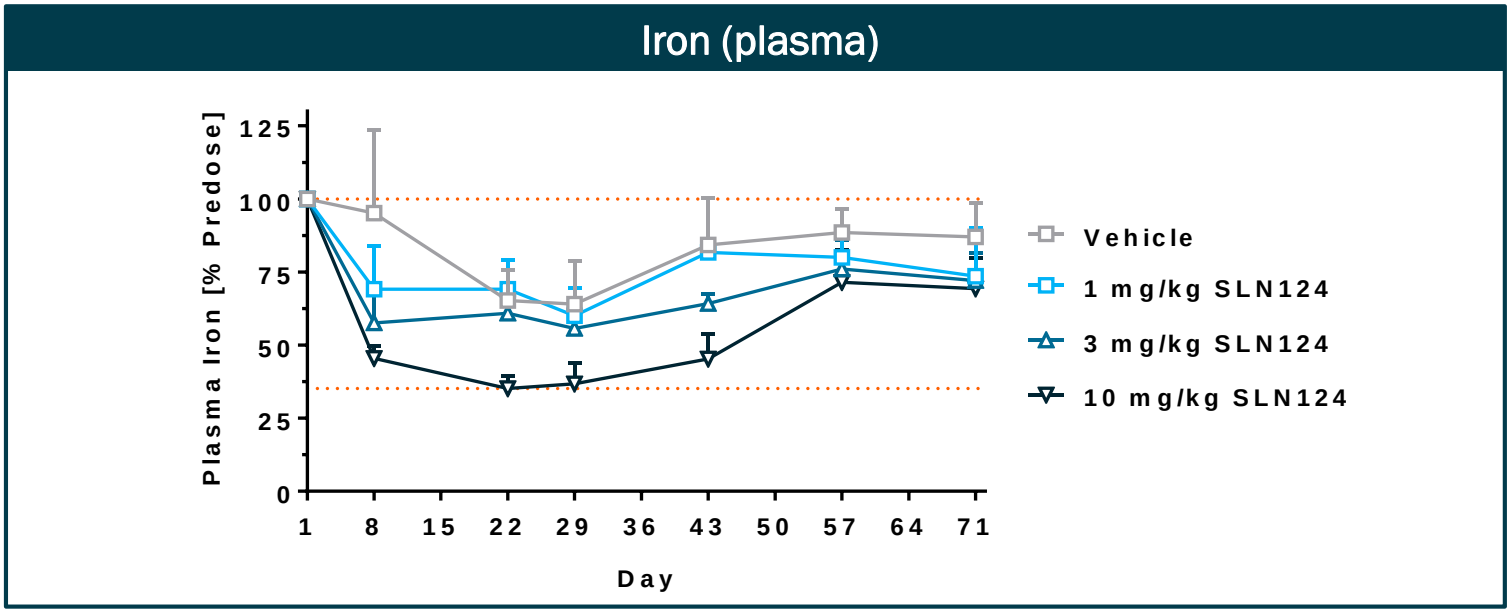
Sustained reduction of circulating iron levels after single administration in non-human primates





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

> Well tolerated with long duration of action

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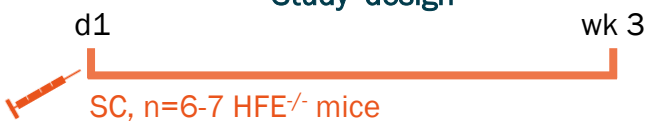
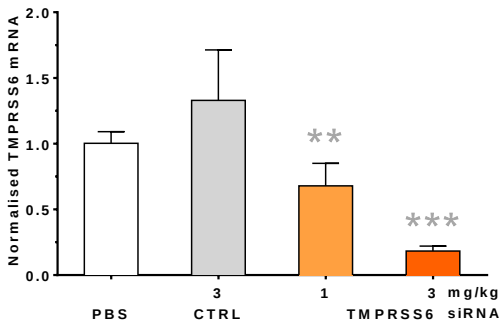
Therapeutic activity of SLN124 in a disease model for hereditary haemochromatosis ($HFE^{-/-}$ mice) - 1/2

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

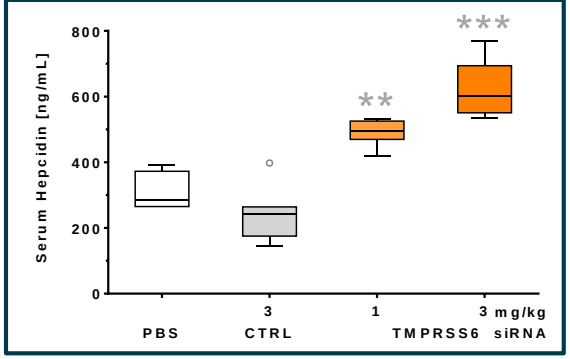
Study design



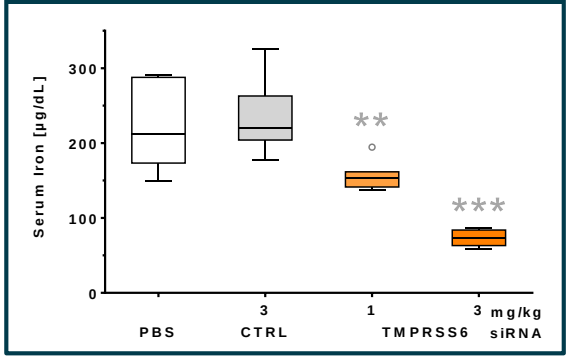
TMPRSS6 mRNA (liver)



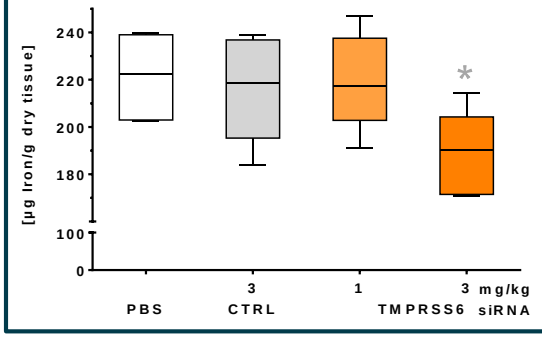
Hepcidin (serum)



Iron (serum)



Iron (kidney)



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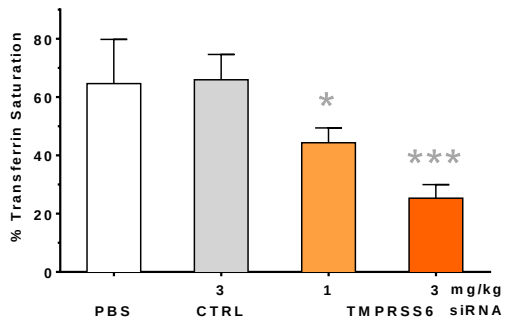
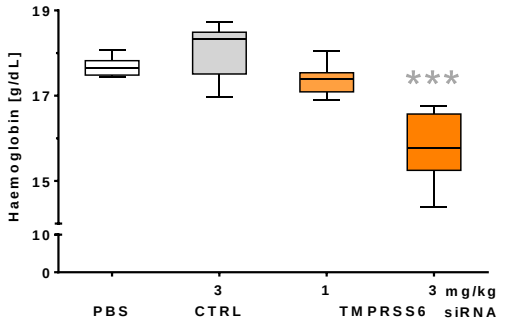
Therapeutic activity of SLN124 in a disease model for hereditary haemochromatosis ($HFE^{-/-}$ mice) - 2/2

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

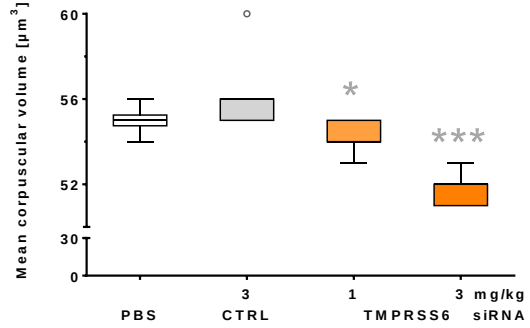
Transferrin Saturation



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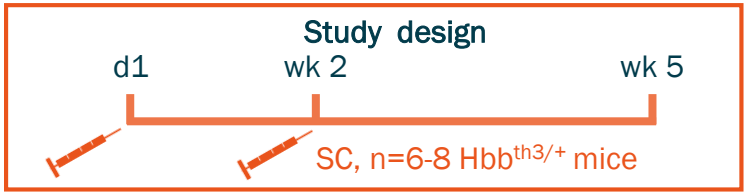
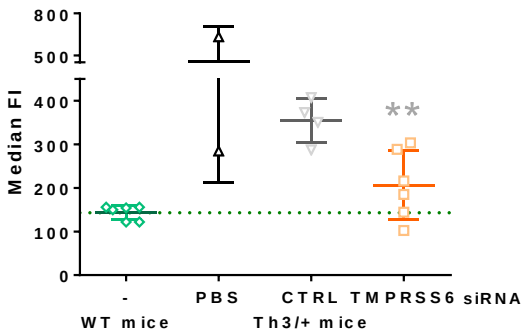
SLN124 normalizes ROS species & improves RBC parameters in β-Thalassemia disease model

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

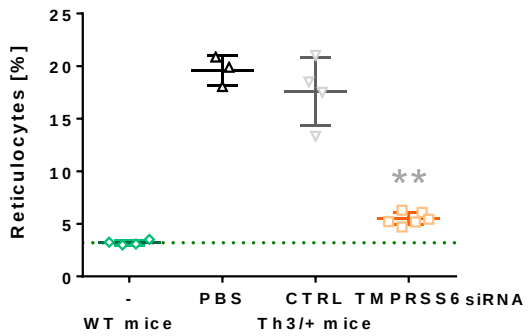
HUDSON INSTITUTE OF MEDICAL RESEARCH



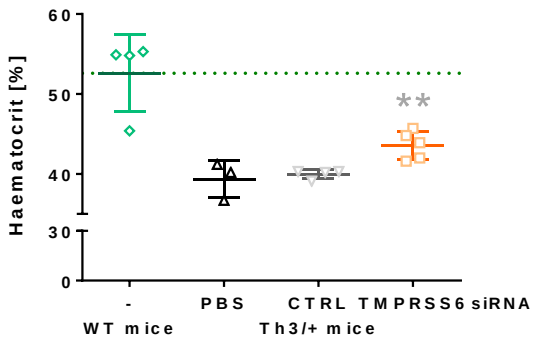
Reactive oxygen species (ROS)



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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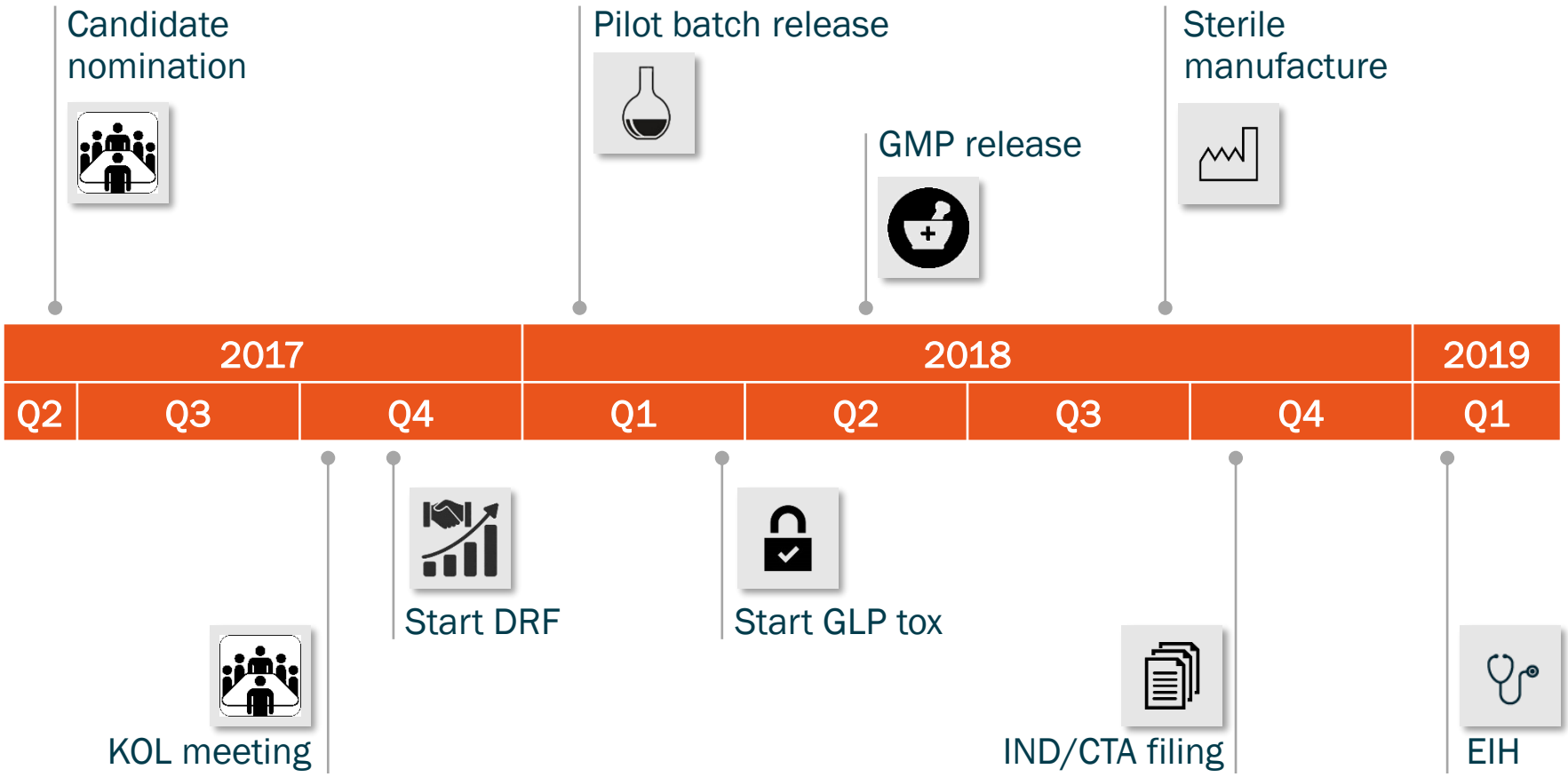
SLN124 development timelines – key milestones



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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SLN226
for the treatment of alcohol use disorder

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SLN226 for the treatment of alcohol use disorder

GOAL

> Provide an effective & safe novel treatment option for patients with alcohol use disorder (AUD)

RATIONALE

> Target ALDH2, a validated target for alcohol aversion therapy, with a GalNAc-siRNA molecule providing a highly specific, effective & safe option through inhibition of the ALDH2 gene expressed in hepatocytes

CURRENT STAGE

> Preclinical development with plans to enter clinical development in Q2/2019*

*potentially with partner

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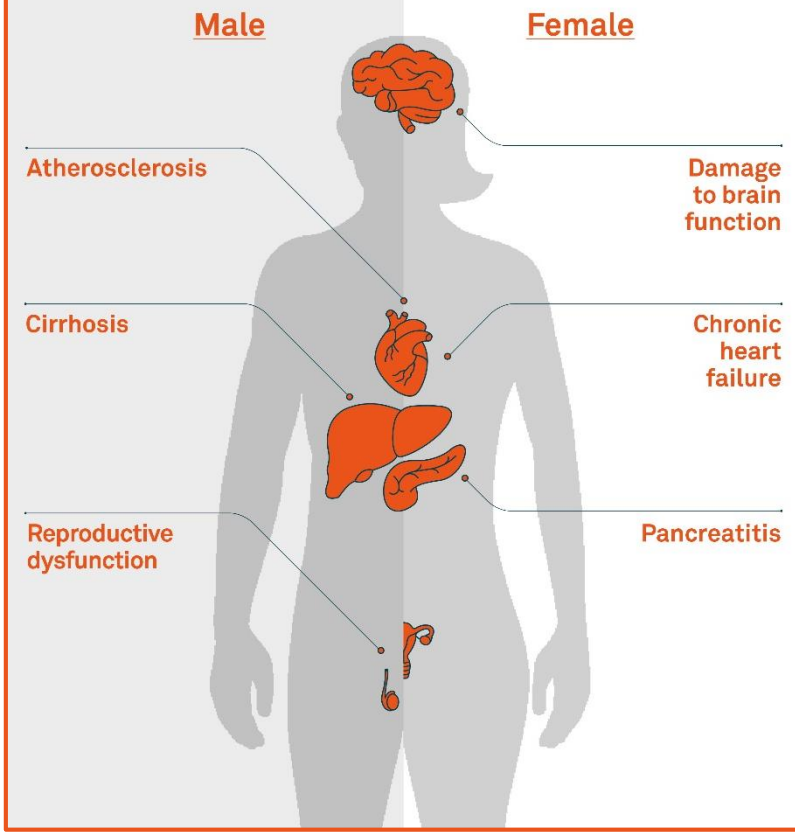
Alcohol use disorder facts - 1/2

Long term effects of alcohol abuse



Consequences of alcohol abuse

> Liver damage
> Cardiovascular complications
> Gastrointestinal damage
> Central & peripheral neurological symptoms
> Anxiety, depression, suicidal tendencies
> Negative impact on social life

Alcohol abuse & physiological dependence on alcohol is a global problem with tremendous impact on health, society and economics

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Alcohol use disorder facts - 2/2

- Chronic alcohol abuse leads to **alcoholic liver disease (ALD)** – spectrum of conditions including **hepatitis** and **cirrhosis** which may eventually require **liver transplantation**
- One third of all liver transplants due to ALD (~4,000 per year); 6-month abstinence rule while waiting for liver transplant

Abstinence is the key requirement for successful resolution of alcohol use disorder, especially for ALD patients awaiting a liver transplant and for the long-term success of the transplant

- Primarily managed by **psychotherapy** but around **70% of patients relapse** after therapy
- **Disulfiram** is often included as co-therapy but use is limited due to significant **safety** and **compliance issues**

High medical need for effective & safe treatment options to improve compliance and alcohol abstinence

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Market opportunity of SLN226 (US & Europe)



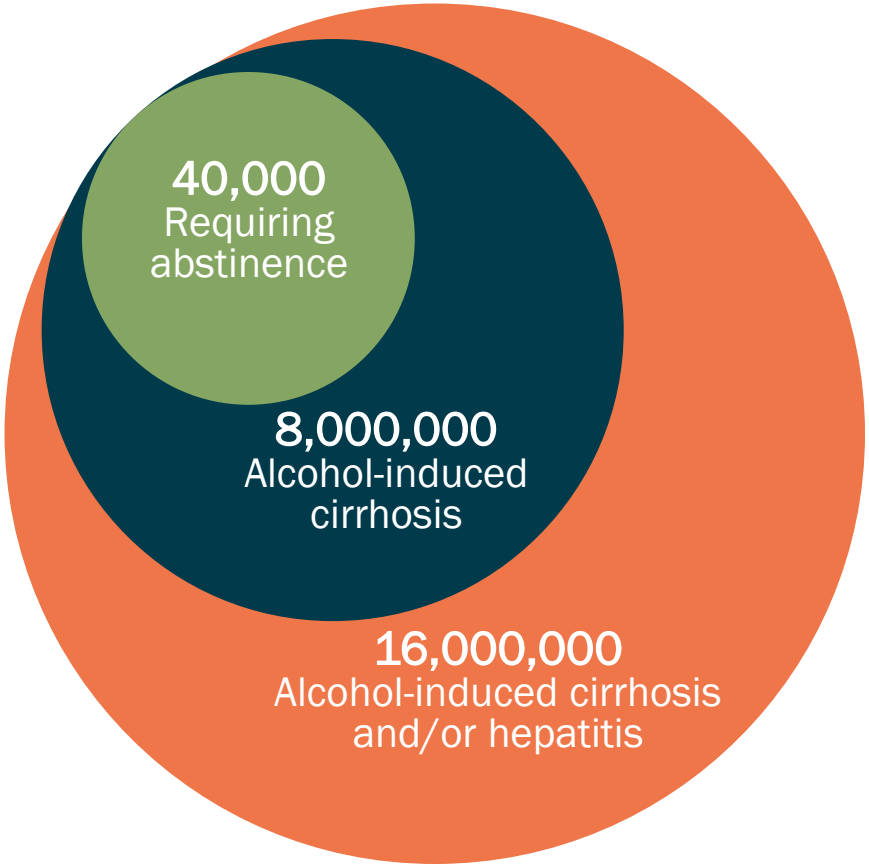
Patients urgently requiring abstinence

- 20-33% liver transplants due to alcohol abuse alone or in combination with viral infection
- Potentially a similar number of patients on the waiting list needing abstinence support
- Expansion to patients with alcohol use disorder strongly committed to abstinence

ALD related disorders

Alcohol-induced cirrhosis

Alcohol-induced hepatitis



- SLN226 has significant potential to aid abstinence in alcohol dependent patients on psychotherapy

ALD – Alcoholic Liver Disease

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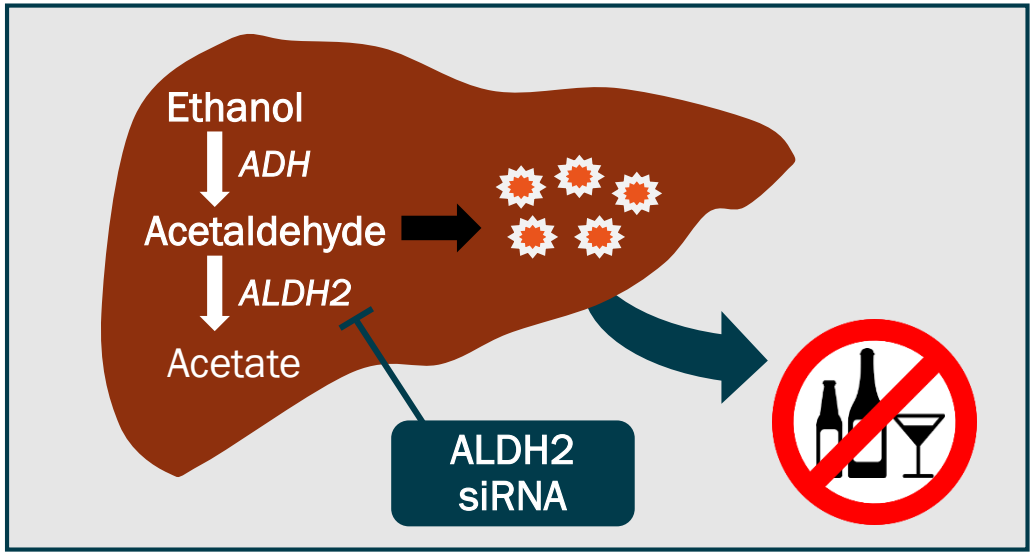
SLN226 mechanism of action

- Alcohol dehydrogenase 2 (ALDH2) is the key alcohol metabolizing enzyme
- Liver is the key organ for ethanol detoxification by ALDH2
- ALDH2 is rate limiting enzyme in the ethanol metabolic pathway



Validated target

- Clinically: ALDH inhibitors e.g. Disulfiram
- Genetically in human subpopulations: alcohol flushing reaction

Silencing ALDH2

1. Acetaldehyde accumulation <u>upon alcohol consumption</u>
2. Unpleasant physiological effects
3. Disrupt addictive cycle & alcohol seeking behaviour
4. Abstinence

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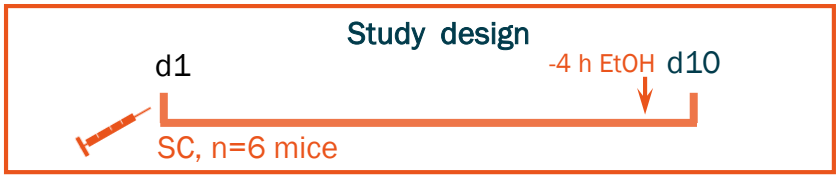
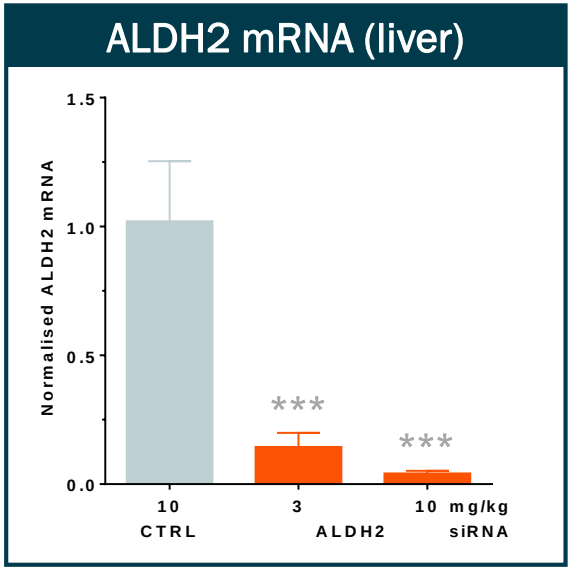
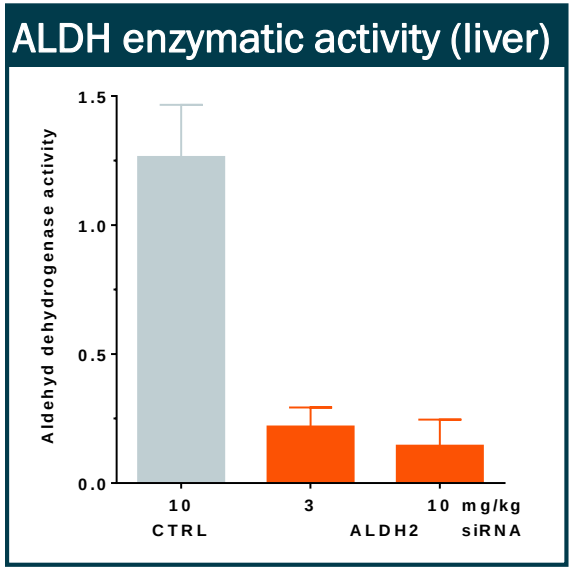
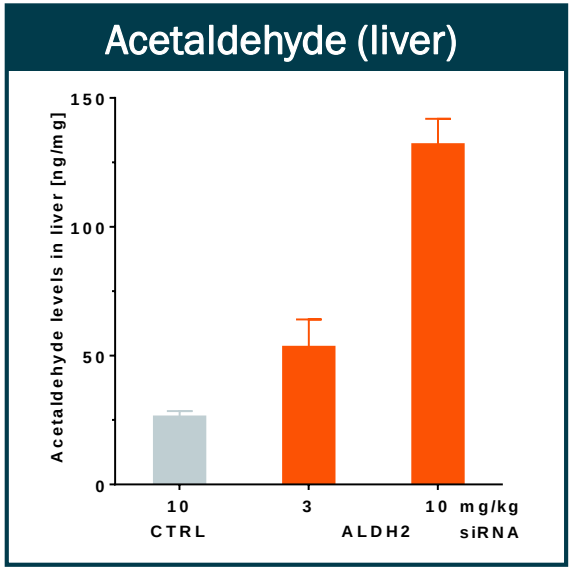
ALDH2 GalNAc-siRNA treatment induces hepatic acetaldehyde accumulation in mice









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

> Single administration results in specific ALDH2 mRNA silencing

> Silencing ALDH2 reduces the capacity of mouse liver to metabolise acetaldehyde

> Proof of mechanism demonstrated

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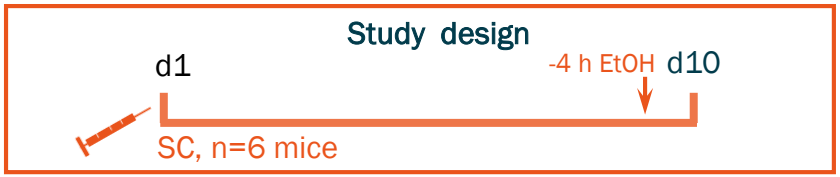
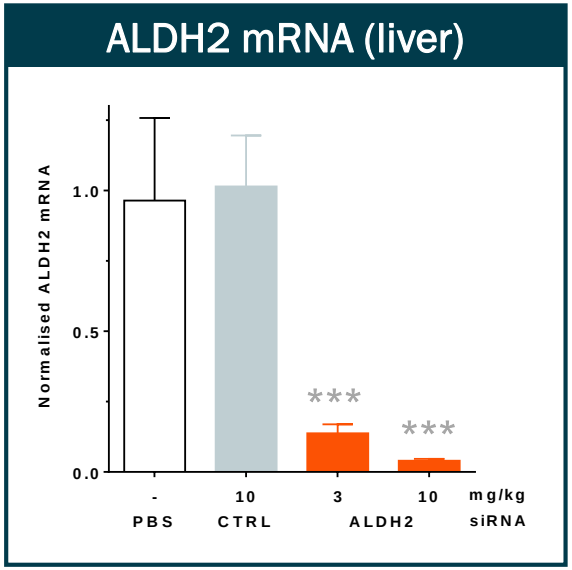
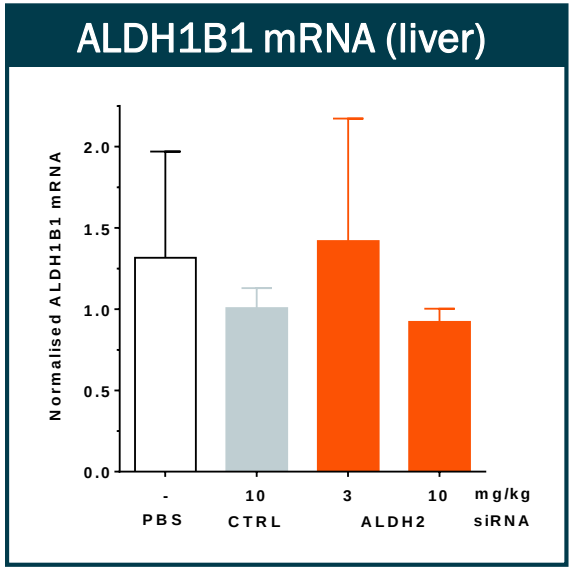
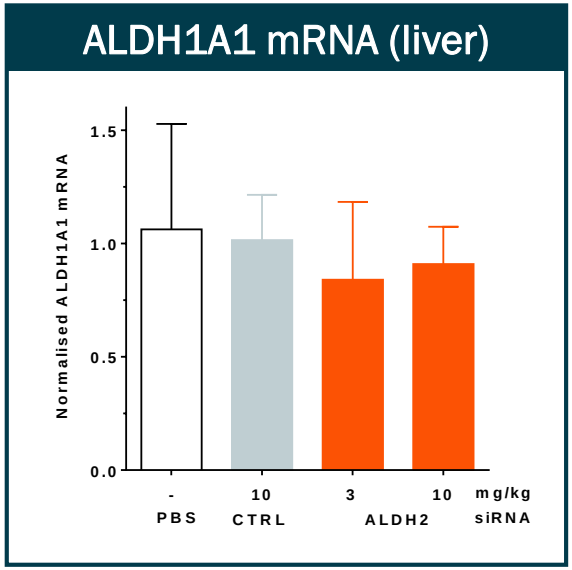
Liver expression of ALDH1 isoenzymes upon ALDH2 silencing in mice









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

> No impact observed on expression levels of alternative isoenzymes, which are capable of metabolising acetaldehyde in mice

> No compensatory mechanism by ALDH1 isoenzymes

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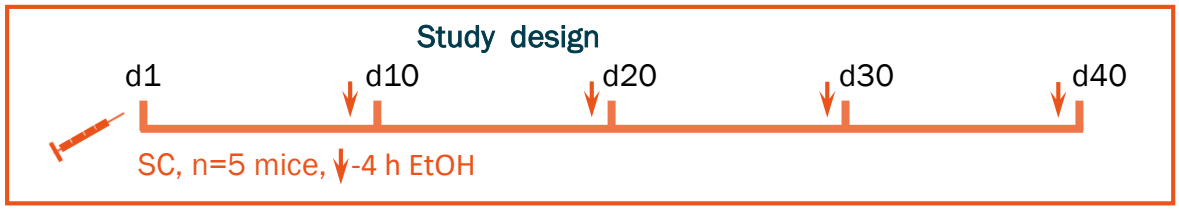
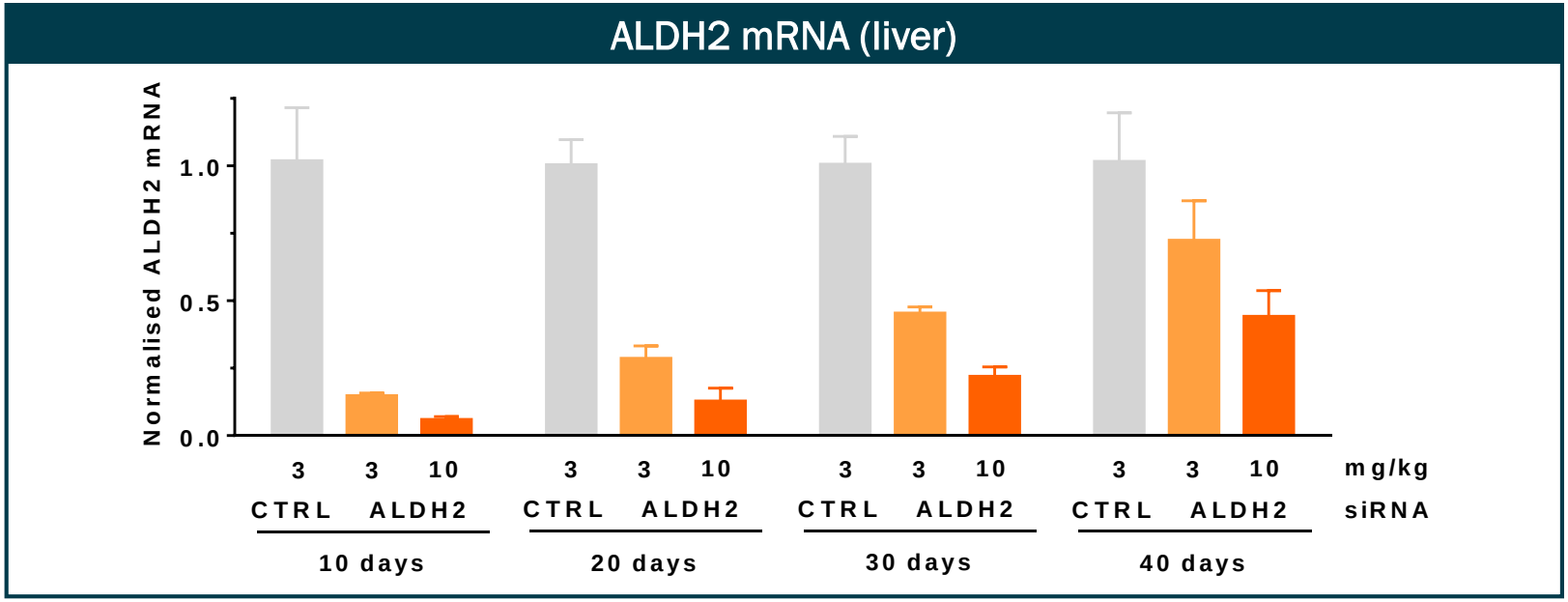
SLN226 reduces ALDH2 mRNA in liver for at least 6 weeks after single administration in mice





> Robust mRNA reduction up to 6 weeks by single administration of 10 mg/kg

> Well tolerated with long duration of action in mice

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Potential of SLN226 as compared to Disulfiram

Reduced side effect potential

(1) Hepatocyte-specific GalNAc formulation (reduction of cardio- & neurotoxic adverse effects)

(2) ALDH2-specific targeting (Disulfiram inhibits ~20 off-target enzymes)

→ Improved safety profile

Higher therapy success rate

(1) KD for weeks advantageous (Disulfiram requires daily in-take causing high percentage of patients to drop out/cheat)

(2) Effective support of alcohol dishabituation and high potential to reduce therapy failure

→ Better patient compliance

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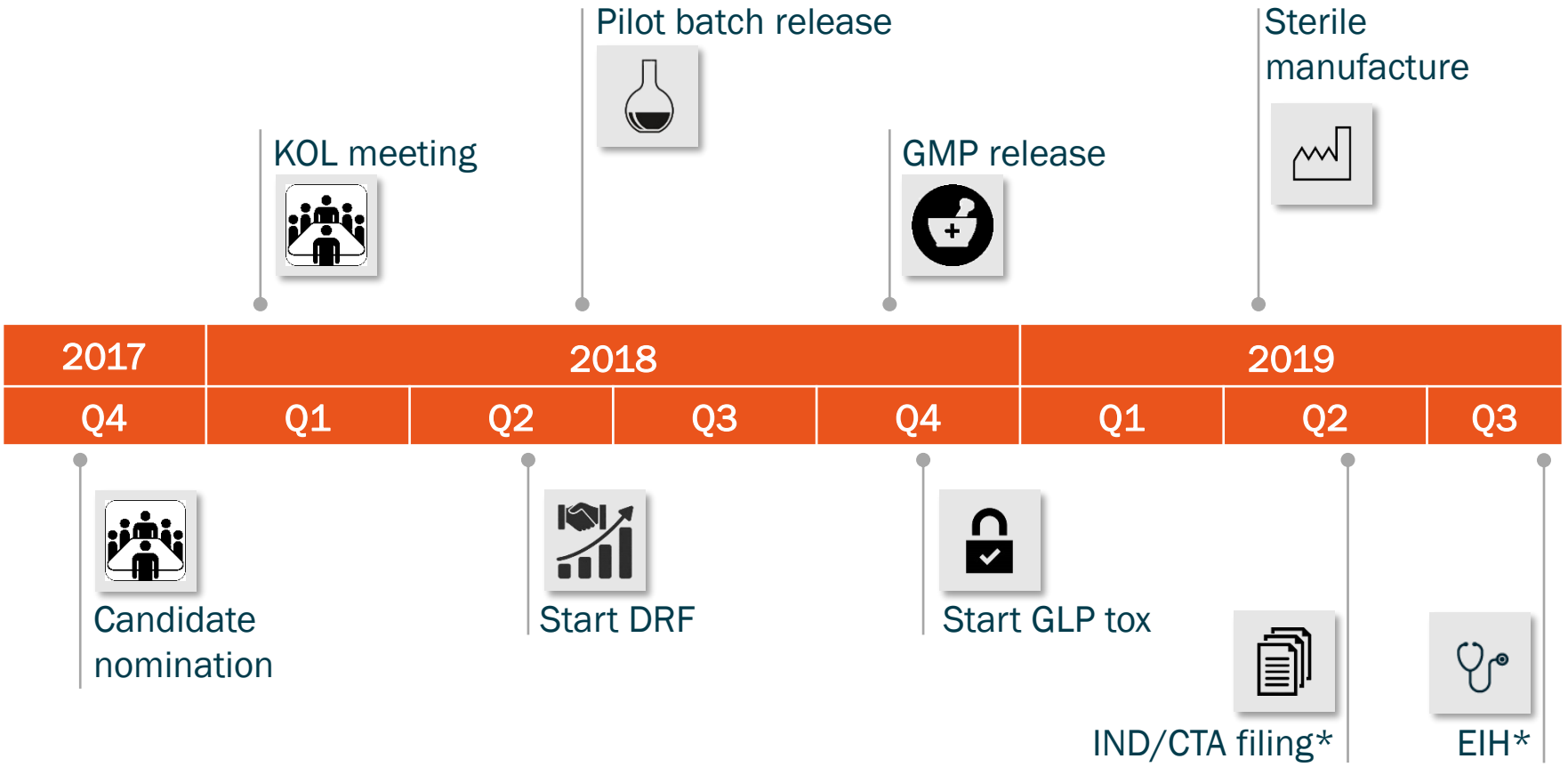
SLN226 development timelines – key milestones



On track for IND/CTA filing in Q2 / 2019

*potentially with partner

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SLN226 - Summary

- Highly potent, selective and long acting GalNAc-siRNA
- Induces acetaldehyde accumulation in mice after single subcutaneous administration
- Currently in preclinical development with plans to enter clinical development in Q2 2019*
- Studies initiated to show therapeutic efficacy in a clinically relevant animal disease model and in higher species

SLN226 represents a highly valuable therapeutic candidate for patients with AUD to maintain alcohol abstinence

*potentially with partner

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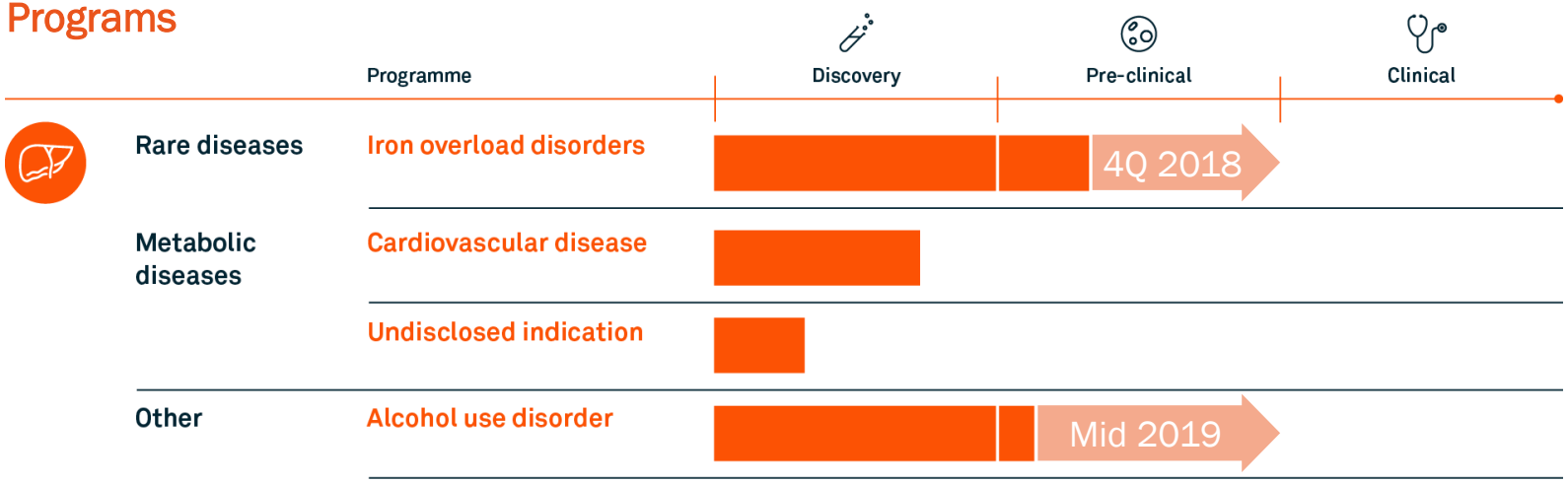
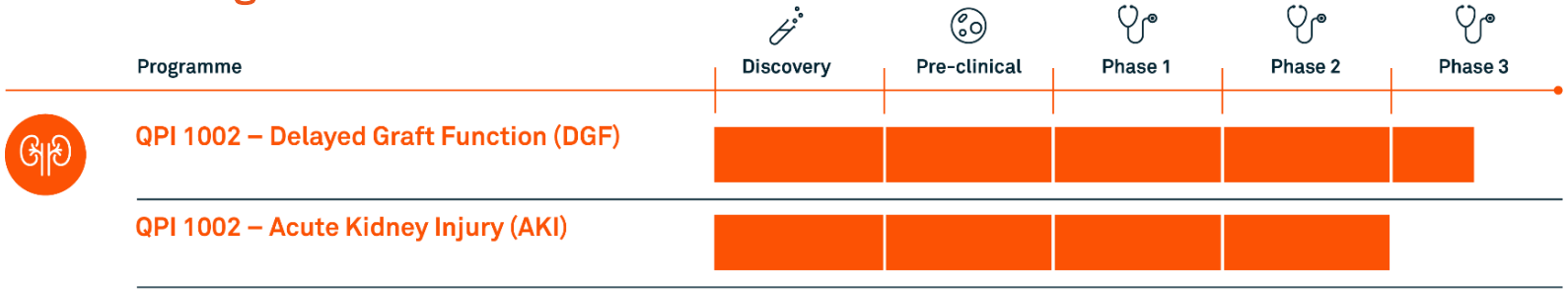
Pipeline

Building a proprietary portfolio, two projects advanced into preclinical development

Our Programs



Out-Licensed Programs



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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

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



Dmitry Samarsky, Ph.D.
Chief Scientific Officer

RIBOBIO



Marie W. Lindholm, Ph.D.
Head of Technology Innovation

Roche
santaris pharma a/s



Torsten Hoffmann, Ph.D.
Chief Operating Officer

ZEALAND PHARMA
proteros
Roche



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

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Silence Preclinical Drug Discovery Team
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Silence Drug Development Team
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