SILENCE THERAPEUTICS

Full Year Results 2017 Presentation

6 MARCH, 2018

Forward Looking Statements

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Silence Therapeutics - Overview



- Developing RNA interference (RNAi) therapeutics, a highly innovative, specific, new class of medicines with life-saving potential for patients with serious and rare diseases
- Only quoted European RNAi drug development Company
- Proprietary platform technology builds on years of scientific research and in-house know-how
- Liver focussed – >7,000 genes are expressed in hepatocytes, many of which are therapeutic targets
- Validating licensing agreement with Quark Pharmaceuticals
- Lead pre-clinical development programme for iron overload disorders (IOD)
- Led by an international, sector-experienced Board and Executive Team
- 30 people in Berlin (R&D) and 15 people in London (Corporate and R&D)
- Explore options to expand our international capital market presence, including the potential for a NASDAQ listing
- Traded on the LSE:AIM – £138 million/$190 million mkt cap* with strong cash runway (£43 million as of 2 January 2018)

* 5 March 2018 price & conversion

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Preliminary Results - Highlights

Operational Highlights

> Generated extensive, multi-faceted, pre-clinical data demonstrating clear proof of biologic mechanism and concept for lead programmes
- Data includes key findings in animal disease models representative of IOD, increasing confidence in Silence's lead candidate

> Licensee Quark announced positive results of a Phase 2 trial
- Met primary endpoints in trial for the prevention of Acute Kidney Injury in patients at high risk following cardiac surgery
- Exclusively partnered with Novartis which has an option for worldwide development and commercialisation in AKI

> Two lead programmes for iron overload disorders (IOD) and alcohol use disorder (AUD) on track to move into clinical development within 18 months
- SLN124 planned to enter clinical development by the end of 2018

> Recruited five high calibre individuals to team
- Leadership roles at both major global pharma and entrepreneurial biotechnology companies, as well as deep RNAi and oligonucleotide expertise

> Commenced UK litigation action against Alnylam Pharmaceuticals and The Medicines Company
- Both companies subsequently sought claims for revocation and declarations of non-infringement in respect of the patent in suit. Silence counterclaimed for threatened infringement of the patent in suit in November 2017
- Likely that all issues between the parties will be heard at a trial beginning on, or around, 3 December 2018

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Preliminary Results - Highlights (continued)

Financial Highlights

> Loss after tax of £1.6 million (2016: £8.4 million)

> Cash and cash equivalents of £42.7 million (2016: £39.0 million)

> Net cash outflow from operating activities £9.6 million (2016: £10.1 million)

> Realised gain on disposals of Arrowhead shares £9.1 million (2016: £nil)

> Significantly bolstered balance sheet cash with sale of Arrowhead shares with proceeds totalling $24.3 million

Post Year-End Events

> New European patent (EP 1857547B) granted further protecting Silence's key siRNA chemical modifications that read widely across the RNAi industry

> Disposal of the final portion of Arrowhead shares with cumulative proceeds totalling $24.7 million and a cash balance of £43 million as of 2 January 2018

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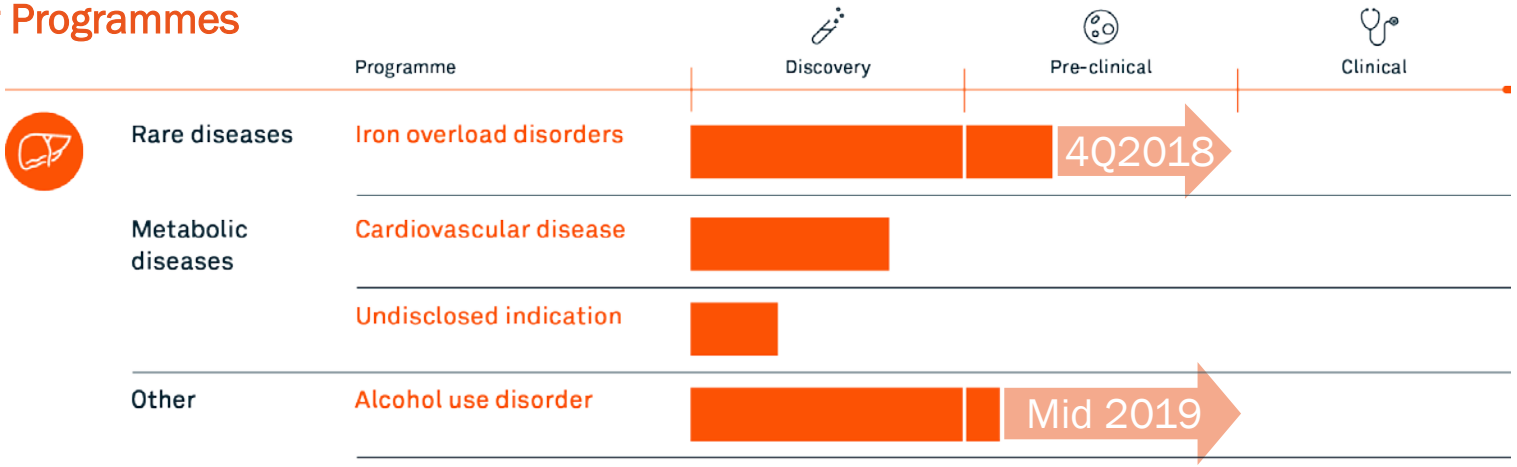
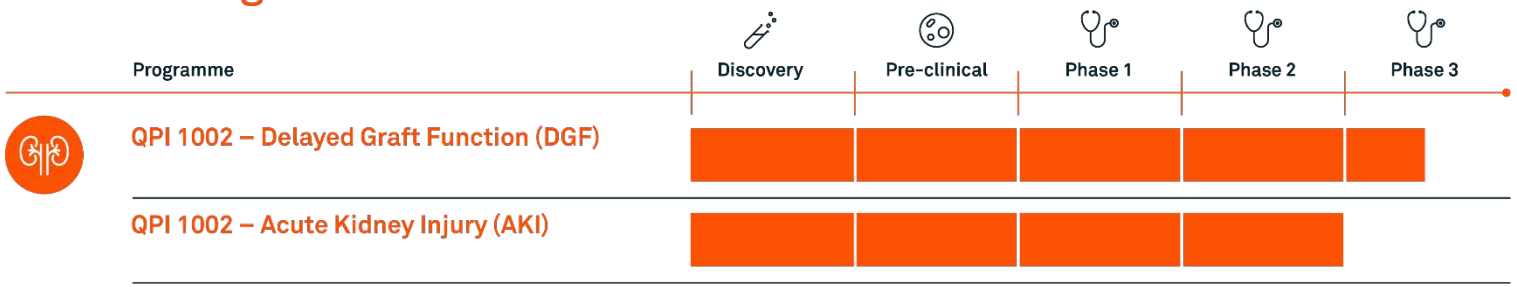
Pipeline - Building a Proprietary Portfolio

Internal programmes advanced into preclinical development

Our Programmes



Out-Licensed Programmes



Quark

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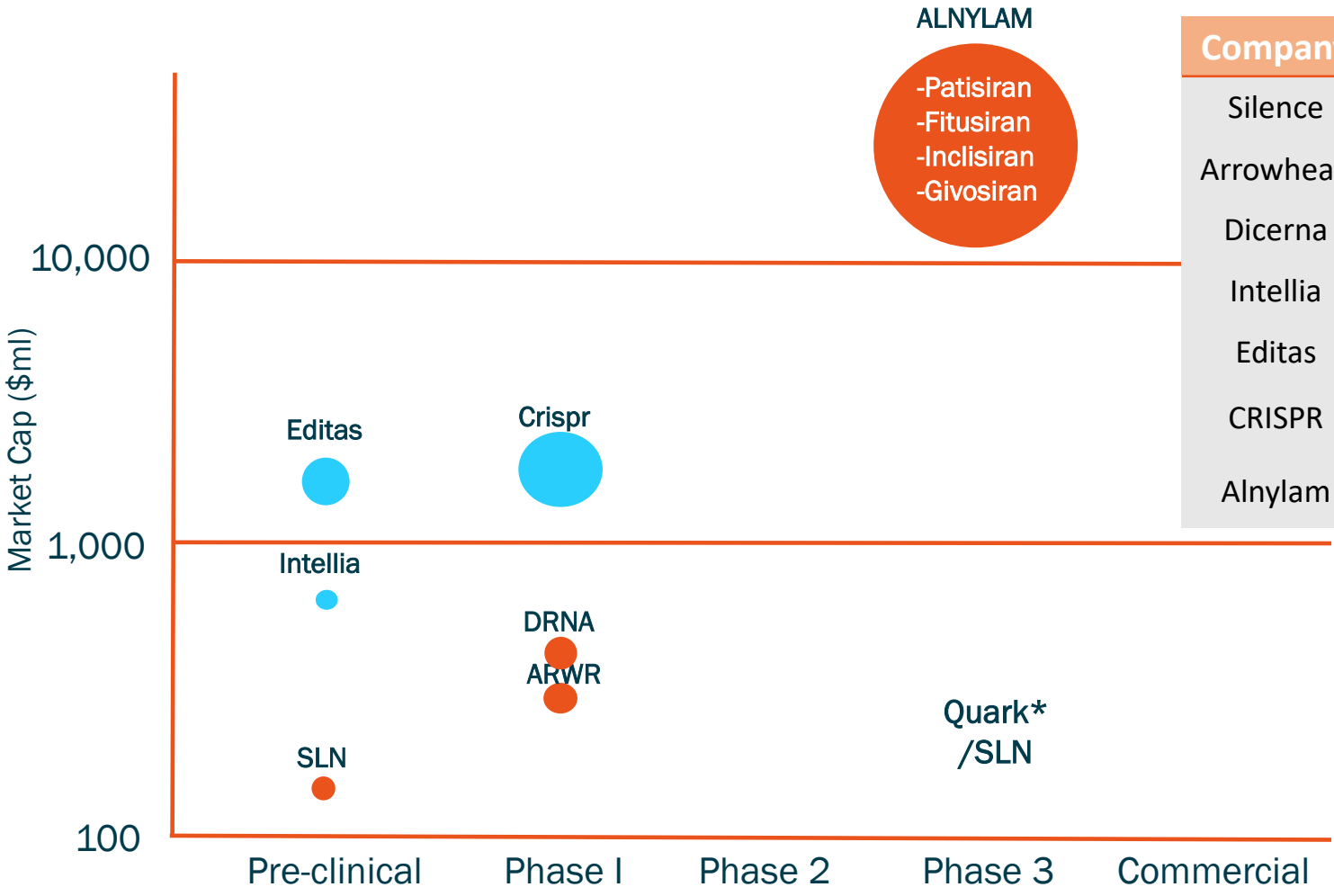
RNAi/CRISPR Companies: Development Stage & Market Cap



Company	Market Cap $M
Silence	192
Arrowhead	562
Dicerna	658
Intellia	941
Editas	1,628
CRISPR	1,765
Alnylam	12,000

** Private*

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Experienced Leadership Team: Strong Background in Discovery & Development of RNA Therapies



Ali Mortazavi,
Chief Executive Officer

Since 2012



Torsten Hoffmann, Ph.D.
Chief Operating Officer

Since 2017



David Ellam,
Chief Financial Officer

Since 2016



Dmitry Samarsky, Ph.D.
Chief Scientific Officer

Since 2016



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

Since 2014



Michael Mulqueen,
Head of BD & Licensing

Since 2017



Alison Gallafent,
Head of Intellectual Property

Since 2017



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

Since 2016



Linnea Elrington,
Head of Human Resources

Since 2017

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

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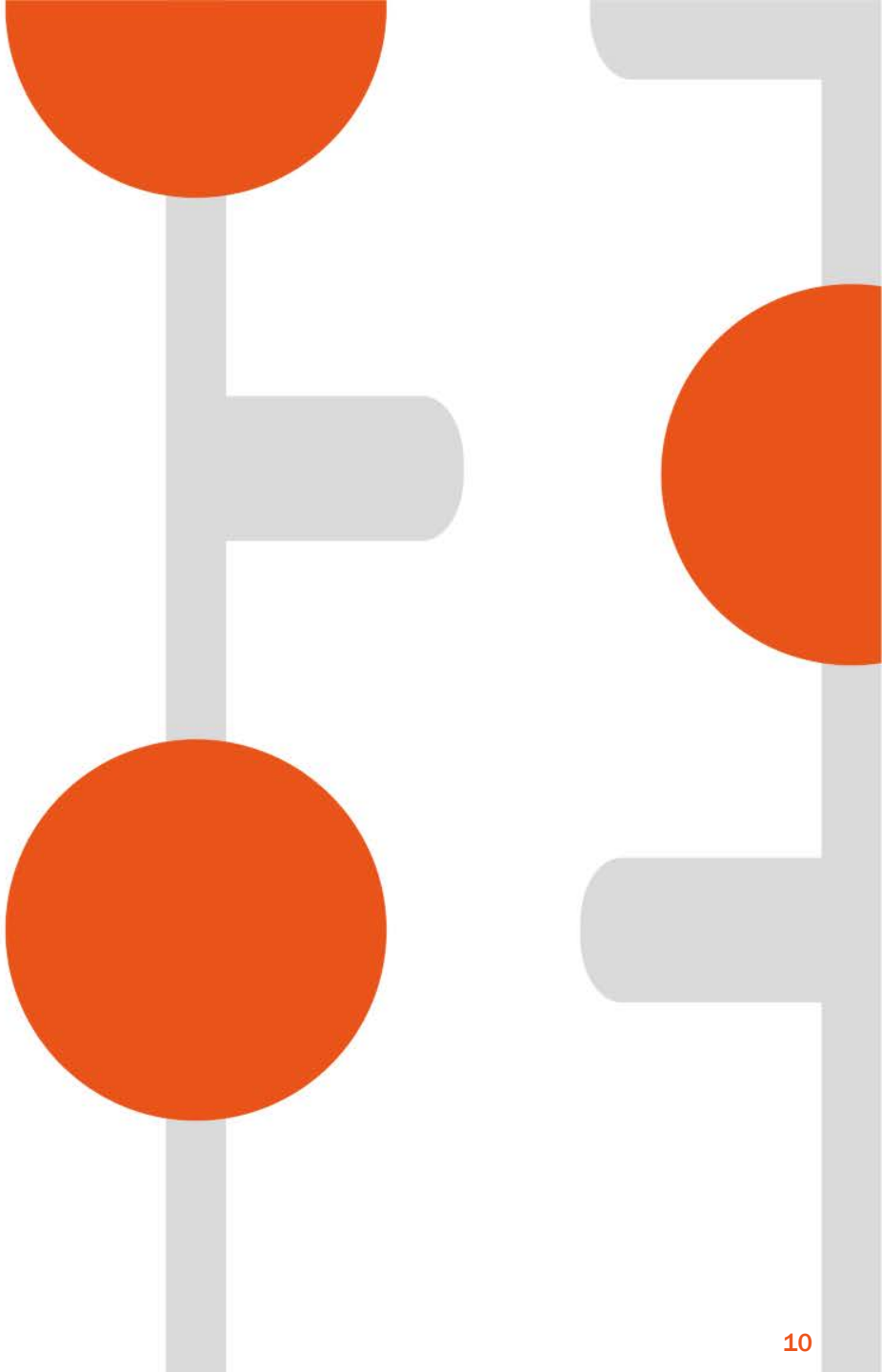
GalNAc-siRNA Platform Technology



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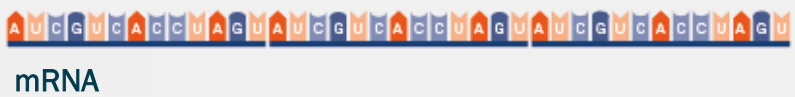
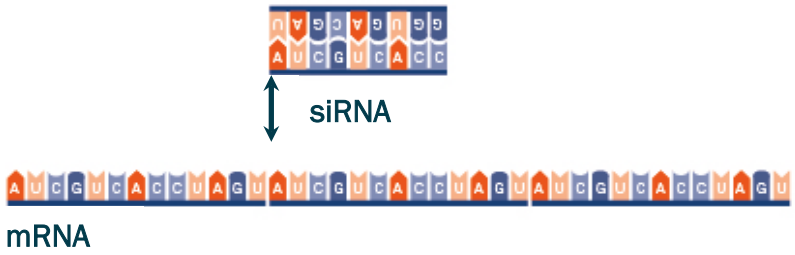
How Do siRNA Medicines Work?

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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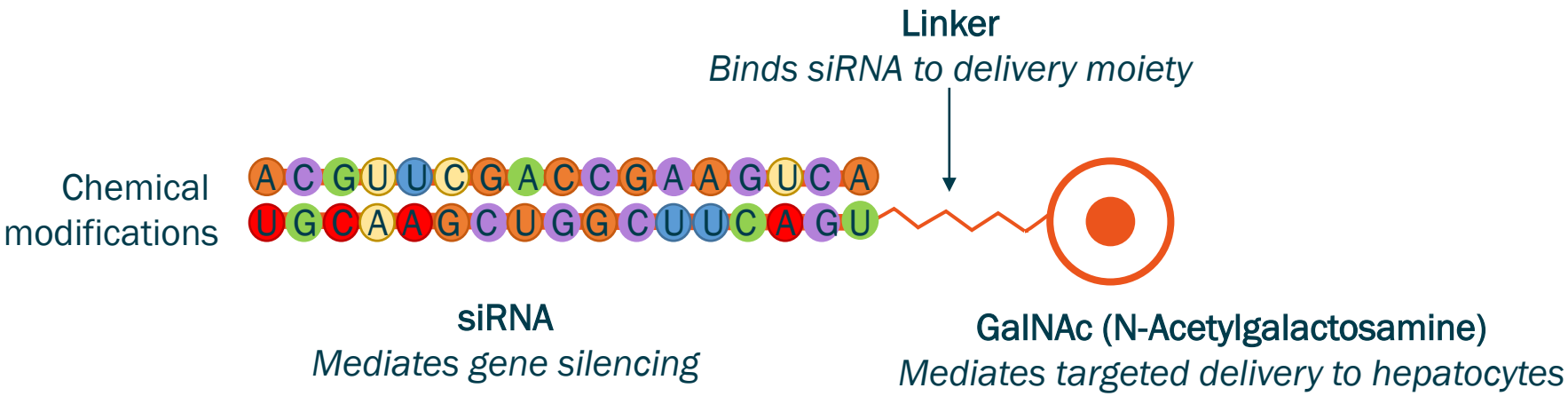
GalNAc-siRNA Medicines

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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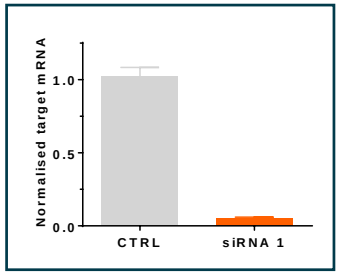
Platform Performance

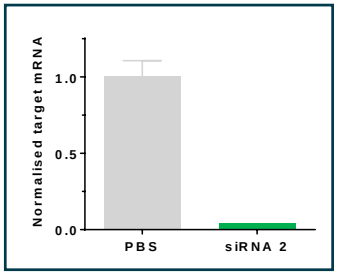
Platform technology: GalNAc-siRNA, able to mediate highly specific gene silencing in hepatocytes (liver) – "Specificity upon specificity"

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

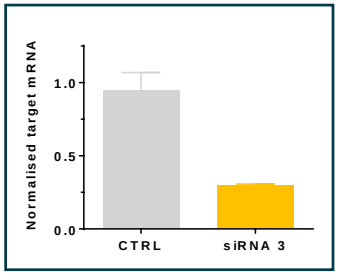
Target 1



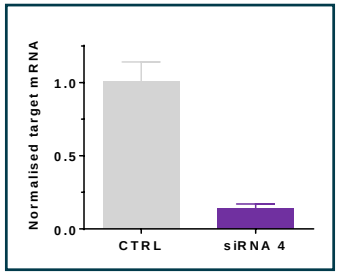
Target 2



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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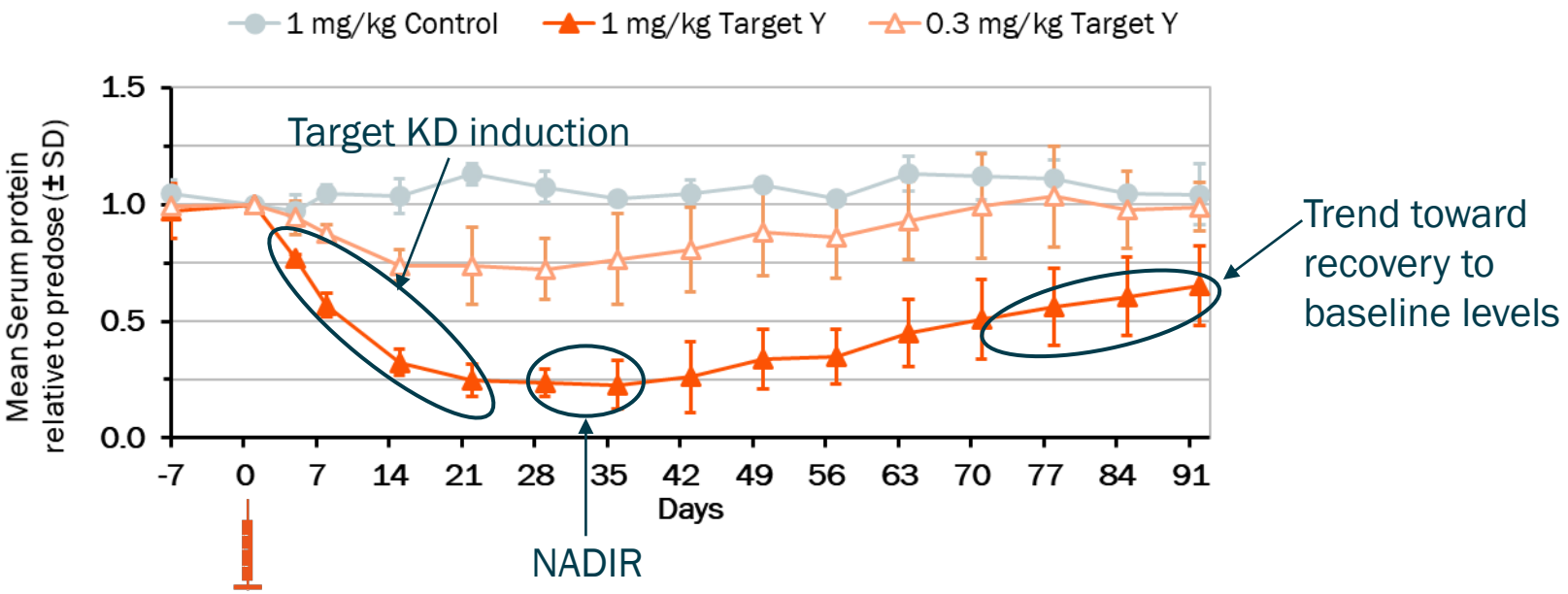
Advantageous Properties of Medicines

- > 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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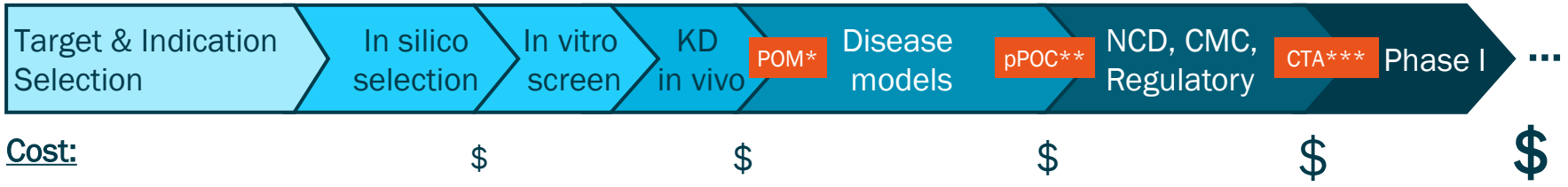
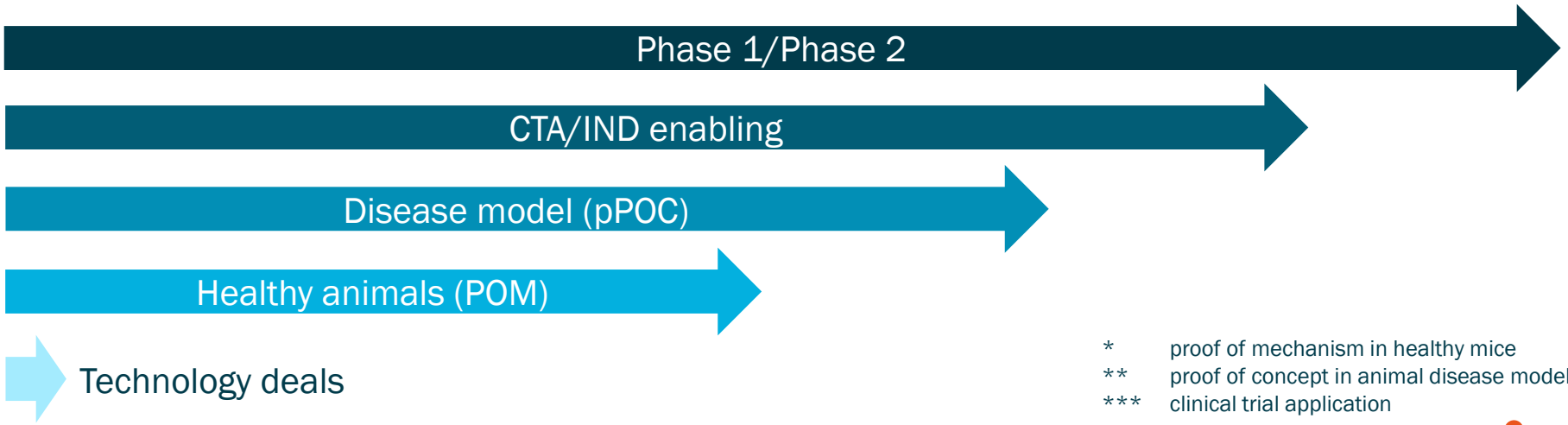
Platform Strategy

~7,000 accessible gene targets…We have the technology and the team to discover and develop a wide range of therapeutics



We intend to strategically partner our programmes at different stages to fully unlock the value of our platform – Rapid path to value creation



* proof of mechanism in healthy mice
** proof of concept in animal disease model
*** clinical trial application

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Intellectual Property - Pioneers in siRNA Chemical Modification Technology Since 2003

We have 13 granted patents and 5 patent applications encompassing our foundational chemical modification technology in US and Europe



Modified siRNA (example)

> **Chemical modifications of siRNA are required to:** 1) prevent degradation, 2) increase stability and potency, 3) reduce immune stimulation

> **IP validation:** License agreement with Quark Pharmaceuticals, which currently has two late-stage candidates in clinical development using our chemical modification technology

> We believe third parties are infringing under our portfolio and we have:

- Disclosed some of the relevant **competitor products**
- Served a claim with the **UK High Court** (defendants: Alnylam Pharmaceuticals and The Medicines Company) to determine whether Silence's European patent protection is entitled to a **5-year extension** for the products named in the claim

> We remain focused on executing our core business of drug discovery, R&D

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SLN124

for the treatment of

Iron Overload Disorders

A case study of our platform

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Treatment of Ion Overload Disorders (IOD)

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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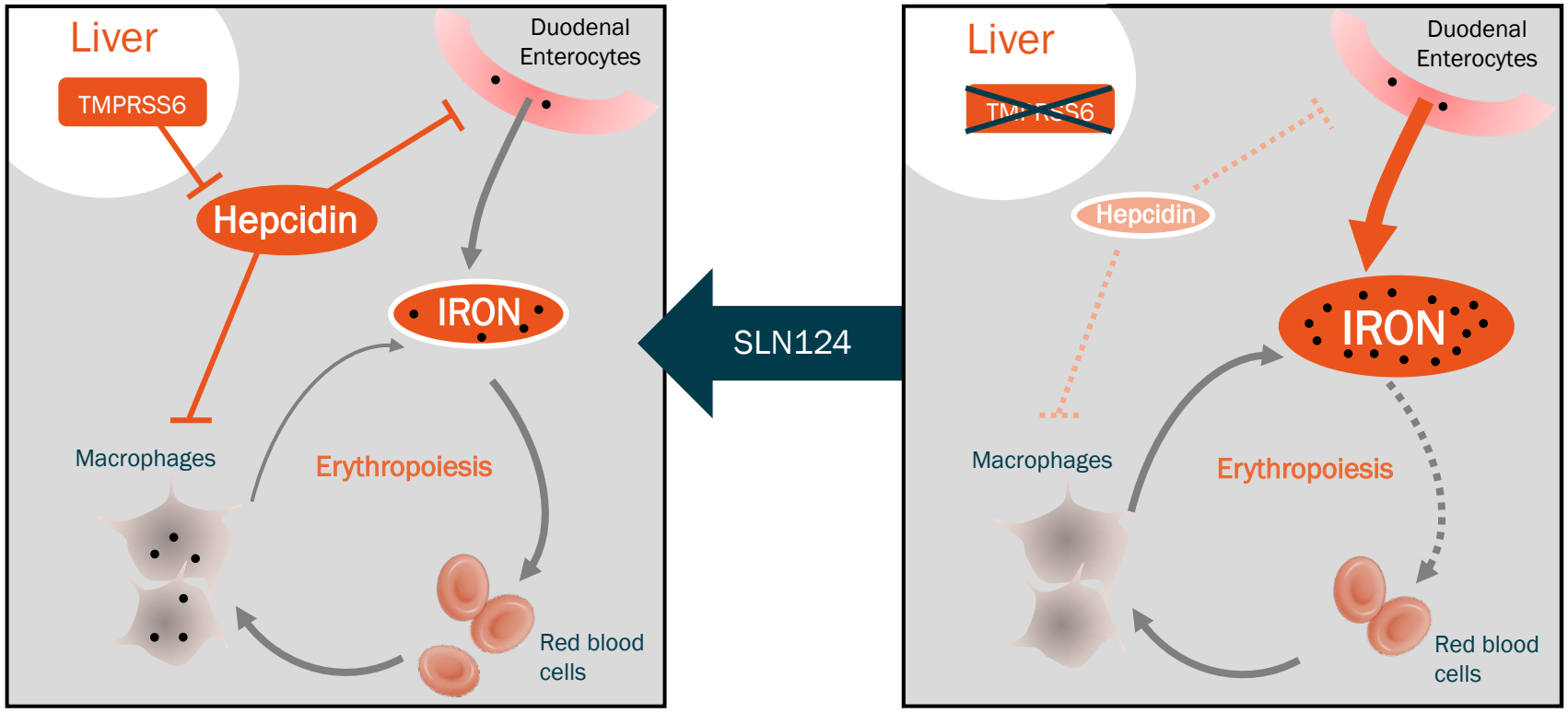
TMPRSS6 is a Negative Regulator of Hepcidin and Plays a Key Role in Iron Homeostasis

Normal hepcidin levels control iron release from cellular stores & intestinal uptake

Low hepcidin levels, as in **β-Thalassemia result in high iron levels** & overload in organs



Silencing TMPRSS6

1. Increases hepcidin levels
2. Reduces iron levels
3. Improves erythropoiesis
4. Reduces organ iron overload

TMPRSS6 = Transmembrane Protease, Serine 6

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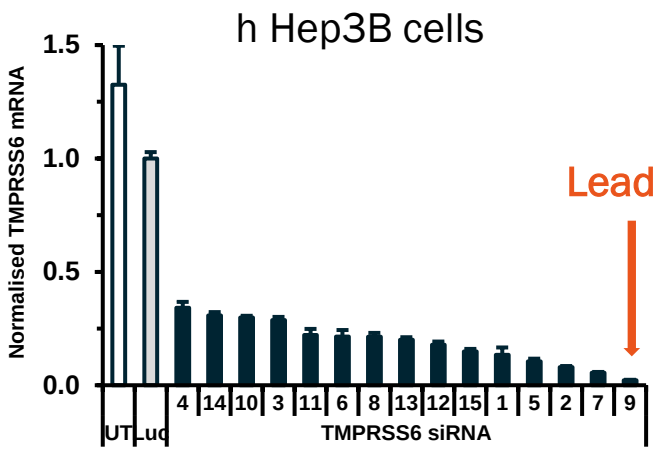
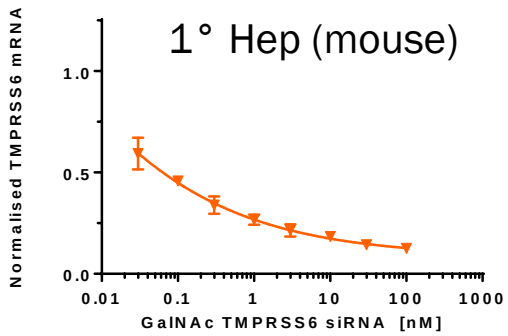
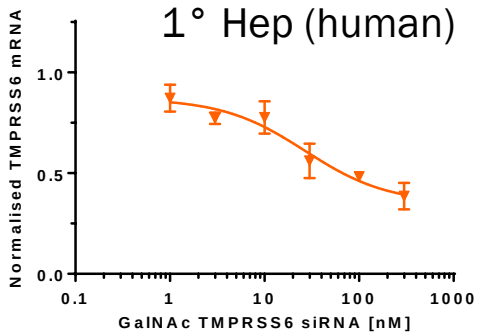
siRNA Screen and GalNAc Conjugate Testing in Primary Hepatocytes

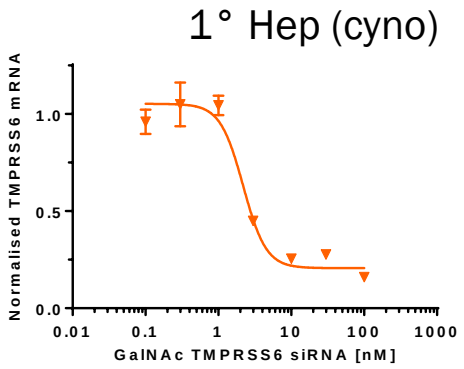
TMPRSS6 mRNA
(in vitro screen – Selected siRNAs)



TMPRSS6 mRNA
(receptor-mediated uptake)







- Lead siRNA for TMPRSS6 identified (picomolar IC50 by transfection)
- GalNAc-siRNA conjugate is functional in primary hepatocytes from different species (mouse, human, cynomolgus)

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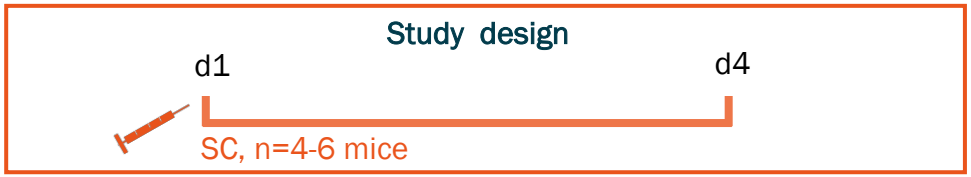
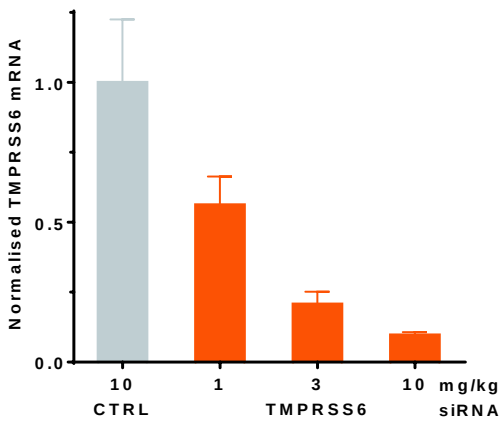
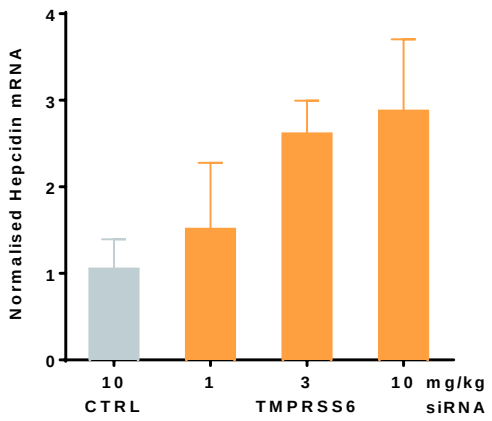
Silencing TMPRSS6 Lowers Serum Iron Levels in Mice



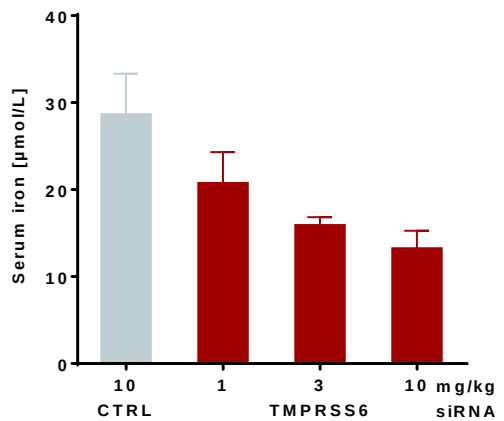
TMPRSS6 mRNA (liver)



Hepcidin mRNA (liver)



Iron (serum)



- Single subcutaneous administration results in specific KD of TMPRSS6
- Upregulated Hepcidin causes reduction of blood iron levels
- **Proof of mechanism demonstrated**

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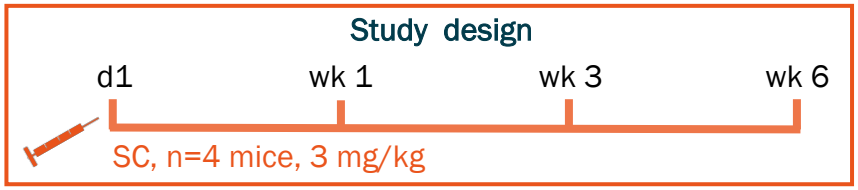
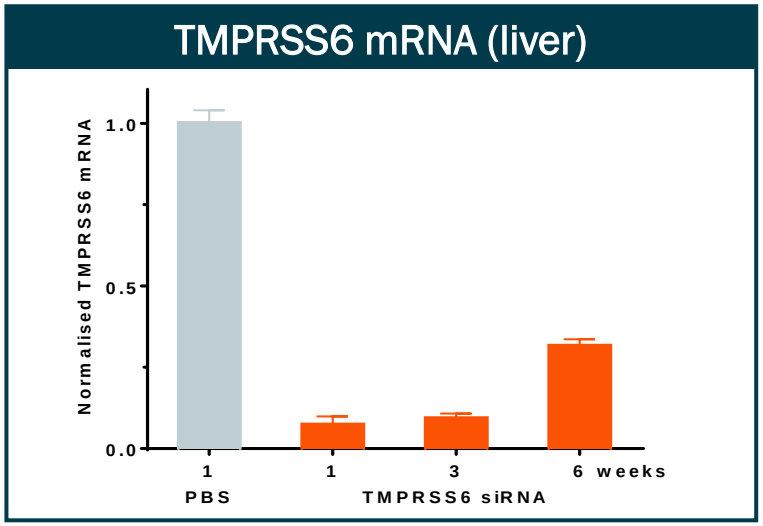
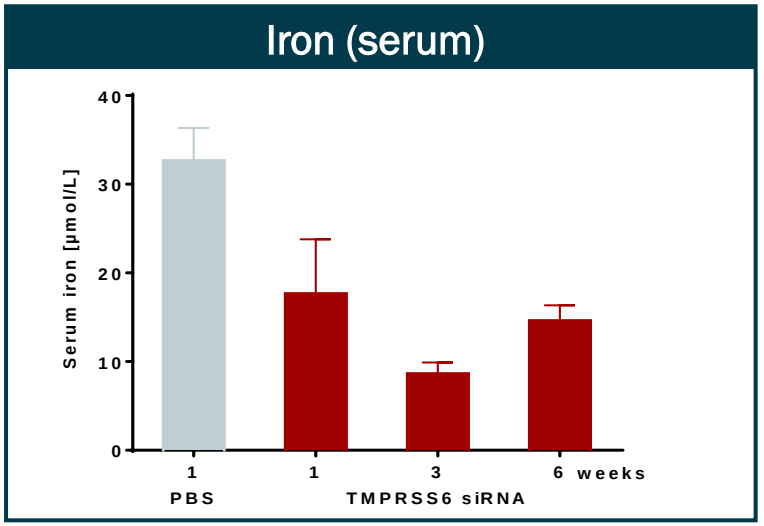
SLN124 Lowers Iron Levels for at Least 6 Weeks After Single Administration in Mice







> 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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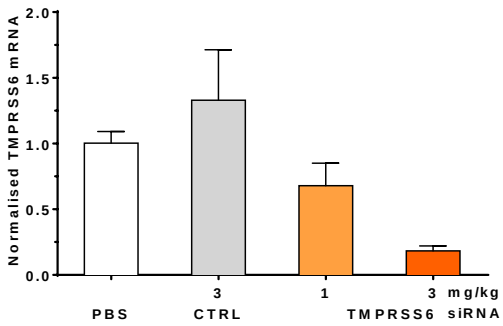
Therapeutic Activity of SLN124 in Iron Overload Model (HFE -/- mice)

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

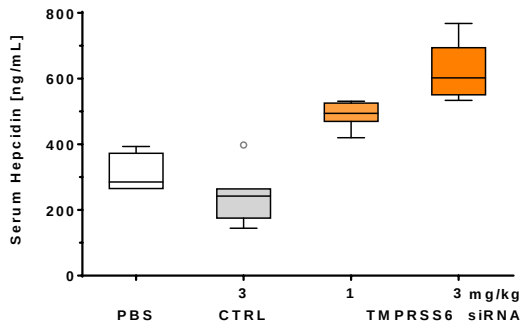
Study design



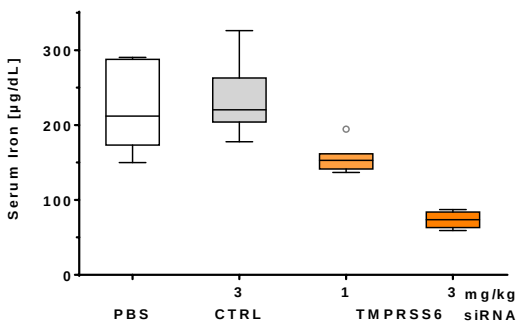
TMPRSS6 mRNA (liver)



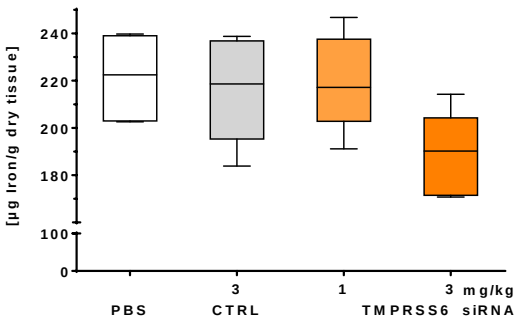
Hepcidin (serum)



Iron (serum)



Iron (kidney)



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

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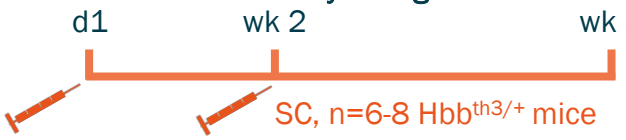
SLN124 Normalises ROS Species & Improves RBC Parameters in β-Thalassemia Disease Model

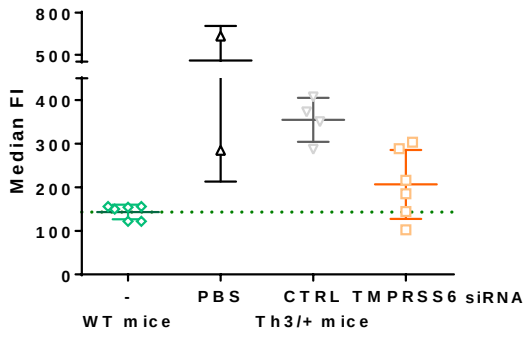
Collaboration with
Prof. J. Vadolas & Dr. Grigoriadis
Monash Medical Centre/Melbourne, Australia

HUDSON INSTITUTE OF MEDICAL RESEARCH

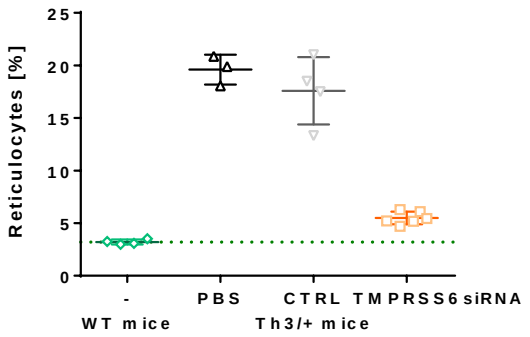
Study design



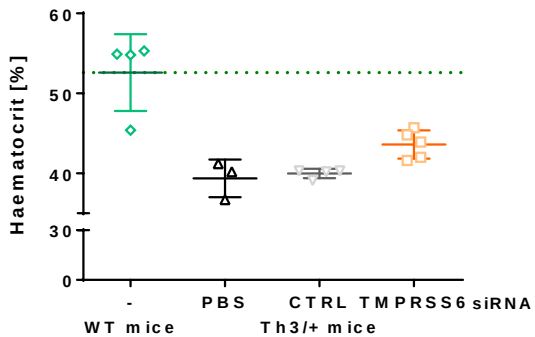
Reactive oxygen species (ROS)



Reticulocyte proportion



Haematocrit



> Normalisation 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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Feedback by Key Opinion Leaders on SLN124

International KOL workshop with clinical and regulatory experts in the field of iron overload disorders

- High medical need to reduce iron overload and number of transfusions in patients
  - Not met by currently available therapies
- SLN124 has the potential to
  - Reduce systemic iron
  - Prevent organ iron overload
  - Enhance erythropoiesis

... providing a significantly improved therapeutic option and better quality of life for patients living with iron overload conditions, such as β-Thalassemia

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Market Opportunity of SLN124 (US & Europe)



β-Thalassemia intermedia & T. major (TDT)

- Combination with transfusions & chelators to reduce frequency & dose
- Improve erythropoiesis and reduce secondary iron overload burden

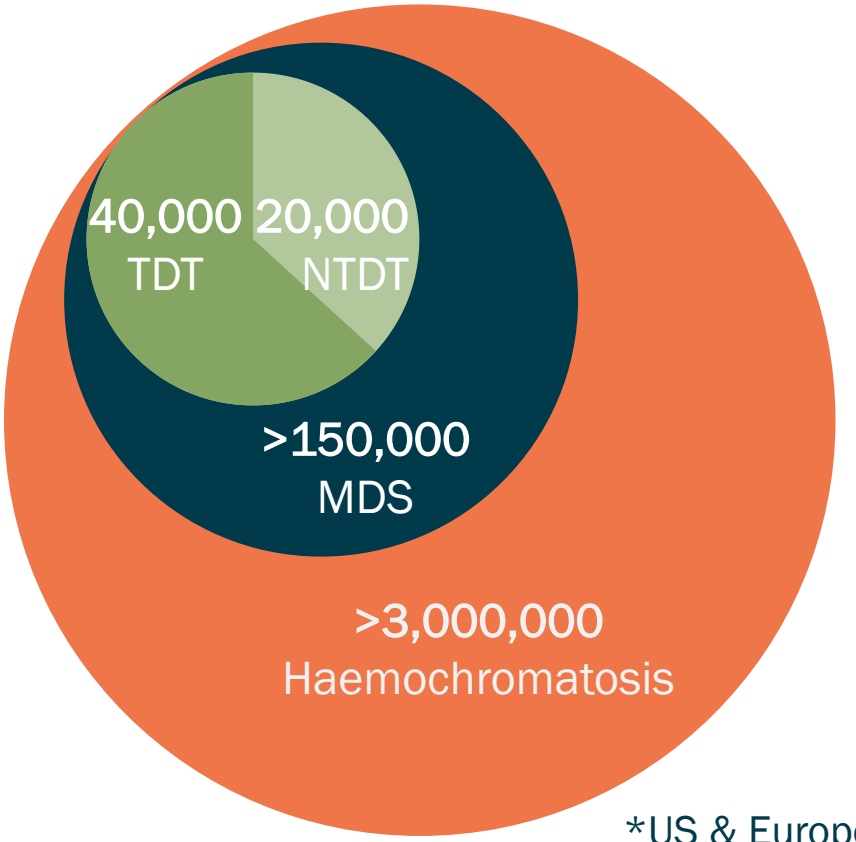
β-Thalassemia intermedia (NTDT)

- 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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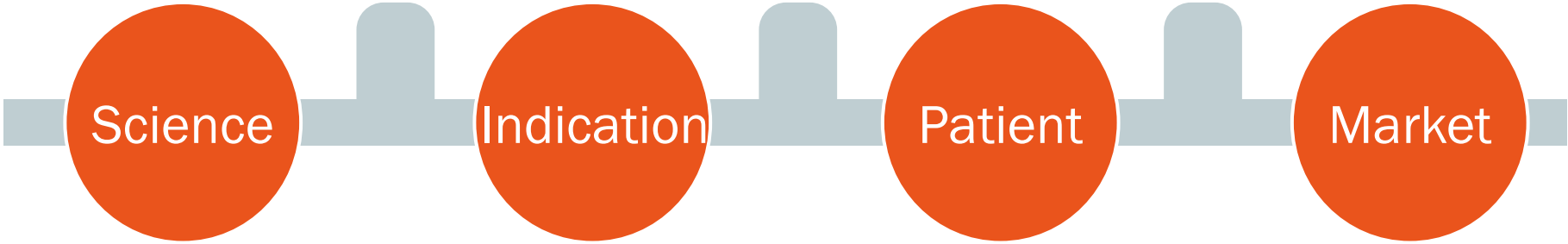
Why we are Excited about SLN124?



What does the Mode of action bring?	How does the science connect to the diseases?	What is the patient benefit?	When and where do we want to market it?
2018: Gene silencing via siRNA is a proven concept	**beta-Thalassemia** **Myelodysplastic Syndromes** Potential for Haemochromatosis	SLN124 has the potential to become an **essential component of the future SoC**	**First In Class** in iron overload
SLN124 has proven to increase hepcidin and **reduce iron plasma levels,** thus restoring iron homeostasis	Central role of hepcidin enables lowering of iron plasma levels, **optimising erythropoiesis**	**QoL parameters** will be improved such as transfusion frequency and drug burden of chelators	**High value product** with peak sales of $600 million (BT) and $3 billion (MDS)
The GalNAc conjugate **targets hepatocytes** in the liver, acting specifically at hepcidin's predominant synthesis site	**Mechanistic claim** – treatment of iron overload disorders	Enables an early treatment option for the **prevention of iron deposition in organs**	**Launch** would be expected by 2024/25 via an Orphan designation
SLN124 is **highly specific** targeting a single gene	**SLN124:** a treatment in the mono- or combination therapy setting as **new SoC**	**Pediatrics and adults will be treated**	A corporate strategy is required to access geographies in the **middle and far east**
		We will work with patient organisations in 2018	We are seeking **commercialisation partnerships**

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SLN124 - Summary

- Highly potent, selective and long-acting GalNAc-siRNA molecule
- Efficacious in lowering blood iron and well tolerated in healthy mice and non-human primates
- Demonstrated therapeutic efficacy in clinically relevant 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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Outlook:
Significant Milestones for the Next 12 months

2018 will be a year of continuity and building upon success to capture value by executing on pipeline development and leveraging its platform

- File clinical trial approval for iron overload by end of 2018
- Add further development expertise to the senior team as pipeline progresses
- Secure further validating collaborations utilising our GalNAc platform technology
- Add new targets to pipeline, and utilise next generation technology
- Continue defensive UK litigation action

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SILENCE THERAPEUTICS

Appendix

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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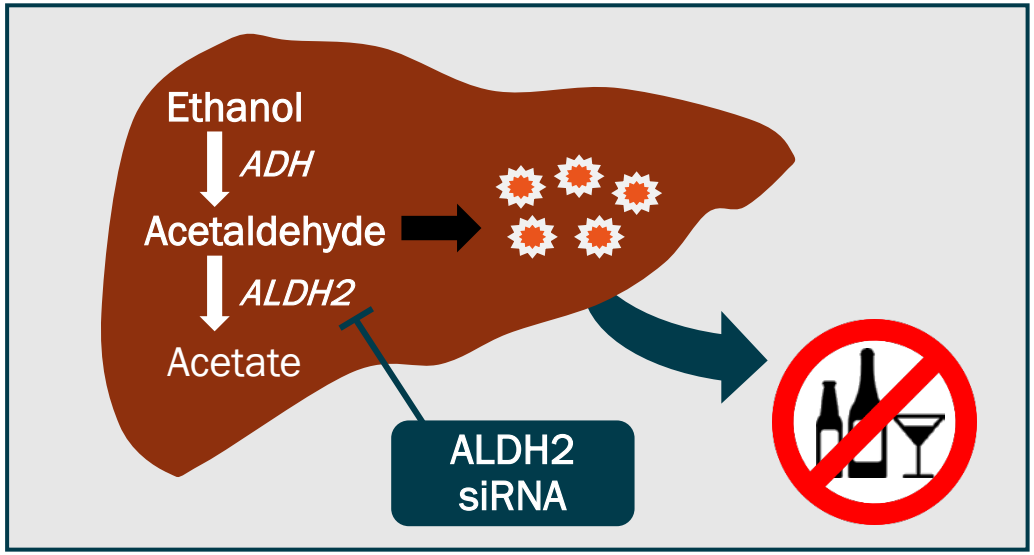
SLN226 Mechanism of Action

- Aldehyde 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 behavior
4. Abstinence

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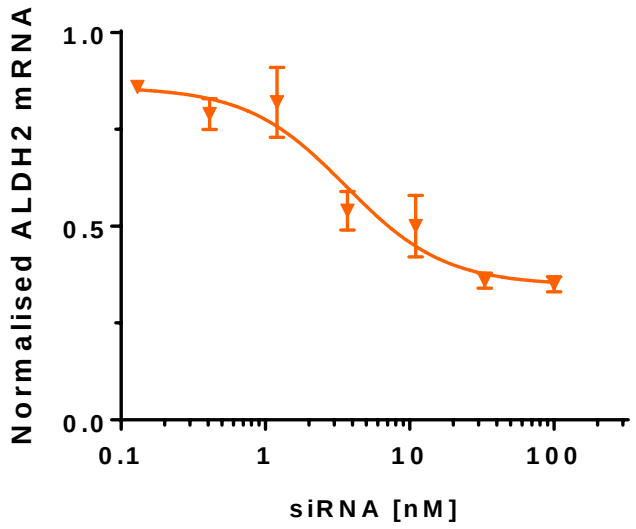
Robust ALDH2 mRNA Knockdown in Primary Hepatocytes

- Bioinformatic-based selection of siRNA sequences by proprietary algorithm and screen for functional activity
- Several sequences identified which potently inhibit ALDH2 mRNA expression in target cells

Human primary hepatocytes





- Receptor mediated uptake & is highly potent in the nM range
- Efficacy in primary hepatocytes (mouse, cynomolgus, human)

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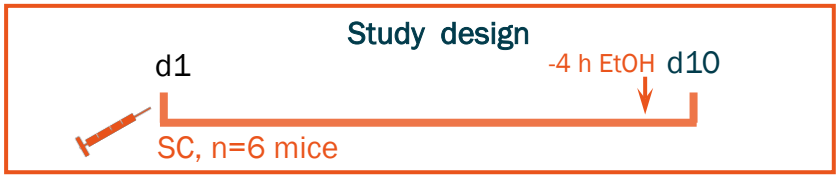
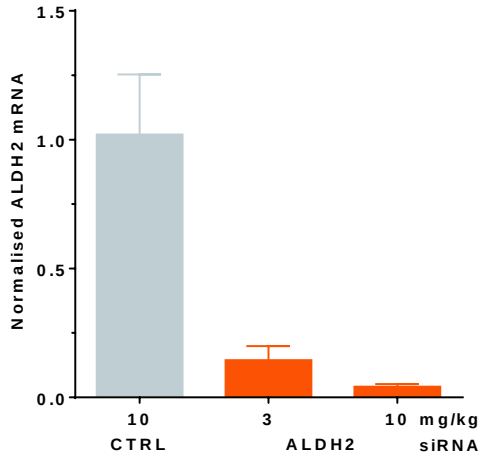
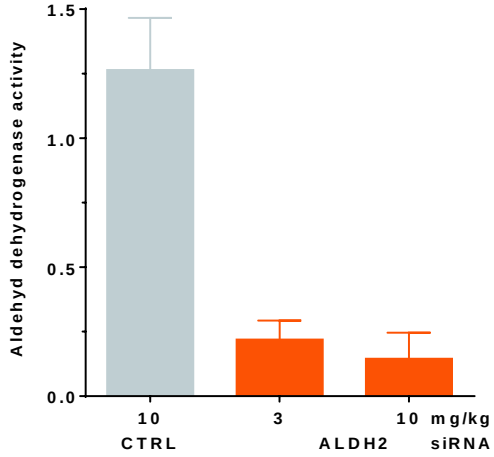
ALDH2 GalNAc-siRNA Treatment Induces Hepatic Acetaldehyde Accumulation in Mice



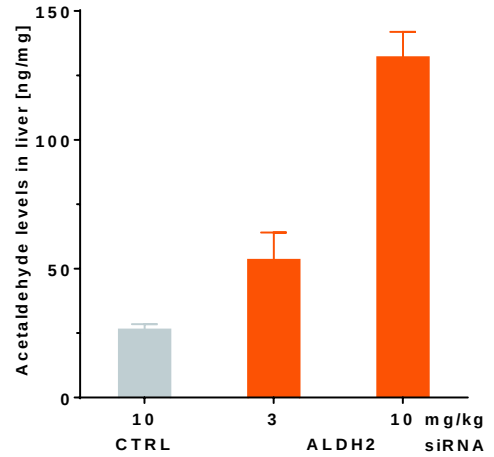
ALDH2 mRNA (liver)



ALDH enzymatic activity (liver)



Acetaldehyde (liver)



> 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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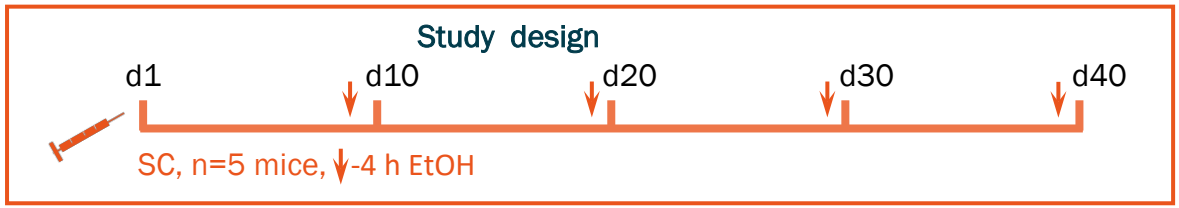
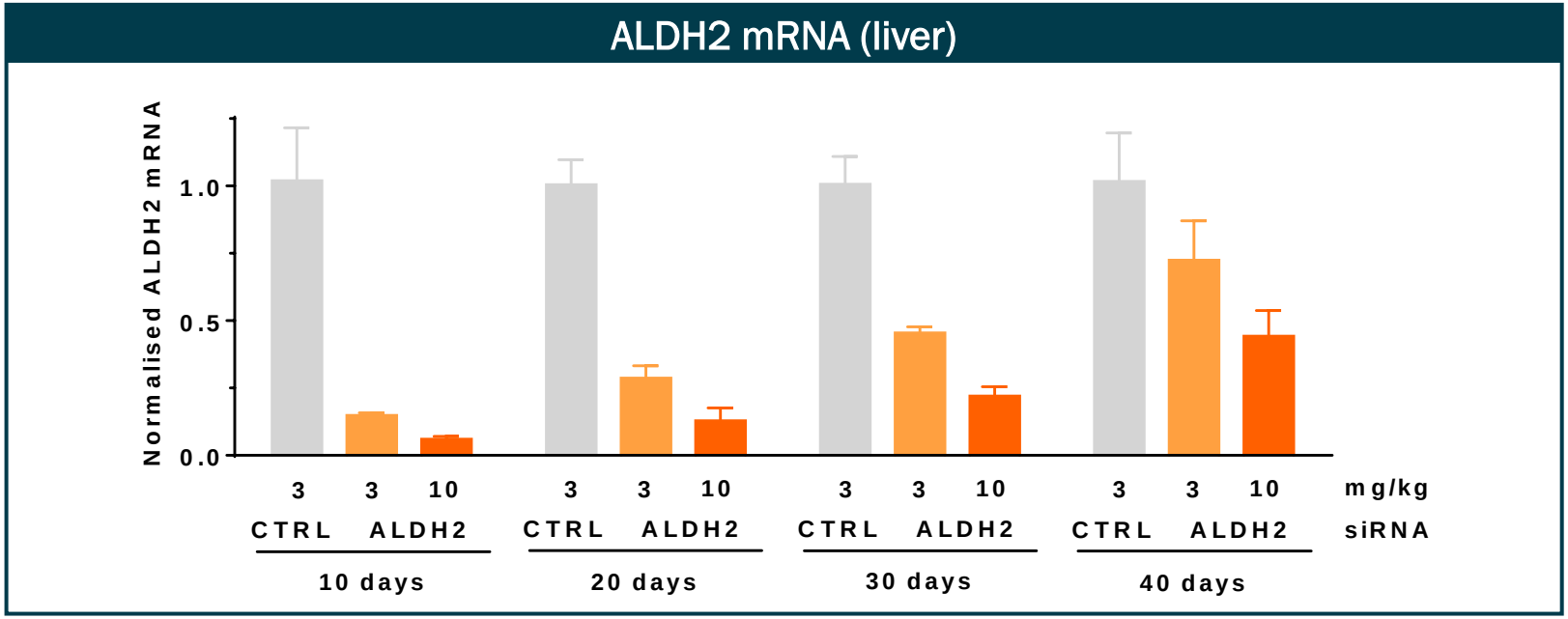
SLN226 Reduces ALDH2 mRNA in Liver 6 Weeks after Single Administration in Mice





> 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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Feedback by Key Opinion Leaders on SLN226

International KOL workshop with clinical experts in the field of alcohol use disorder

- Alcohol abuse & physiological dependence on alcohol is a global problem with tremendous impact on health, society and economics
- There is a clear unmet medical need to become abstinent
  - Not sufficiently met by currently available therapies
- Hepatologists may be more attracted to prescribing SLN226 as an extension to psychotherapy
- SLN226 has the potential to aid abstinence in alcohol dependent patients on psychotherapy

... providing a significantly improved and safe therapeutic option to improve compliance and alcohol abstinence for patients living with alcohol use disorder

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Potential of SLN226 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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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

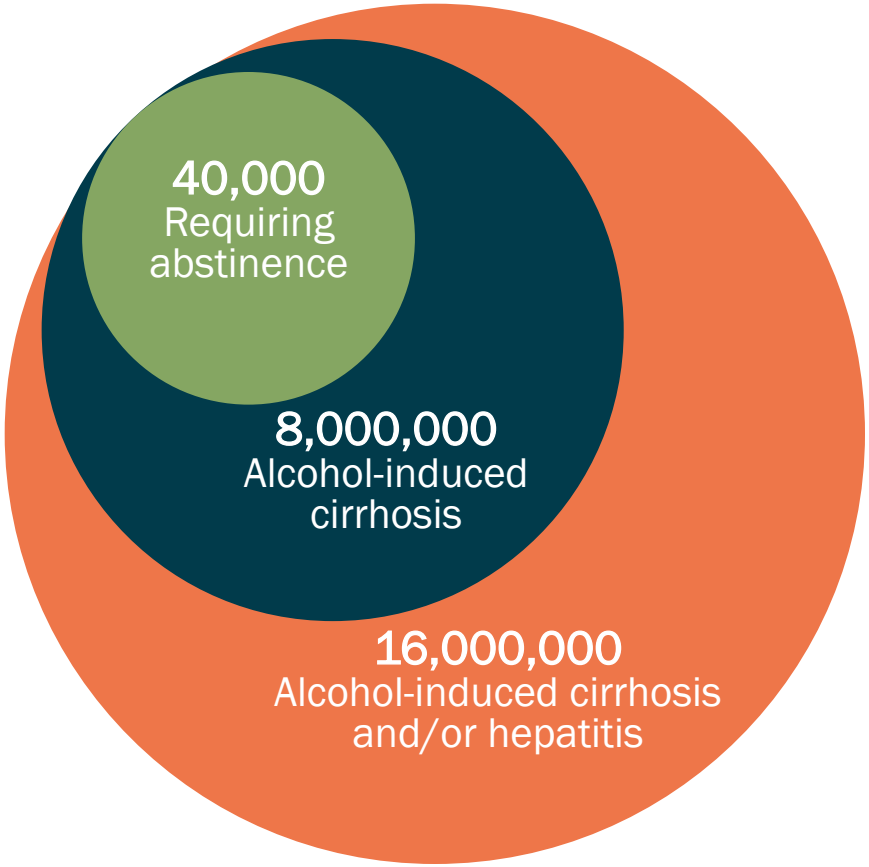
> Potentially a similar number of patients on the waiting list needing abstinence support

> Expansion to patients with alcohol use disorder strongly committed to abstinence

Alcoholic Liver Disease related disorders

Alcohol-induced cirrhosis

Alcohol-induced hepatitis



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

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SLN226 - Summary

- Highly potent, selective and long acting GalNAc-siRNA molecule
- 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 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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