SILENCE THERAPEUTICS

Corporate Presentation
JP Morgan Conference

January 2018

Forward looking statements

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Silence Therapeutics - Overview

- Only quoted European RNA interference (RNAi) drug development Company
- Proprietary platform technology builds on years of scientific research and in-house know-how
- Silence currently focuses on the liver hepatocyte, which expresses > 7,000 genes, many of these are potential therapeutic targets
- Validating licensing transaction with Quark Pharmaceuticals
- Lead pre-clinical development program for iron overload disorders
- 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)
- Traded on the LSE – £139M / $188M mkt cap* with strong cash runway ($58M at 2nd Jan 2018)

* Conversion rate of $1.3503: £1 as of 12/29/17

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RNAi - on the cusp of becoming a new class of therapeutics for patients

RNA interference is a natural pathway that can be harnessed to inhibit the expression of disease-causing genes without altering DNA

AT SILENCE

- Established a competitive **GalNAc-siRNA platform technology** and advanced our pipeline toward the clinic
  - Most advanced program is in iron overload and **first CTA is planned for Q4 2018**
  - Second program in alcohol use disorder is targeting a mid 2019 CTA, potentially with a partner
- Licensee Quark Pharmaceuticals reported positive Phase 2 results in Acute Kidney Injury and continued Phase 3 progress in Delayed Graft Function
- Continued in-house innovation and strengthened patent estate with **European and US patent grants in 2017** and filed multiple patent applications covering additional aspects of our GalNAc-siRNA technology
- Added significant industry-leading talent to the Silence team

IN THE FIELD

- Many years of academic and industry scientific research to-date, unlocking new opportunities
- First positive siRNA Phase 3 readout (Patisiran), validating the field
- Several other late-stage clinical candidates making progress in clinical development
- Renewed big pharma interest in leveraging this platform as part of a broader investment in genetic medicines

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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 programs in a strategic manner
- Add new programs in a risk-diversified manner

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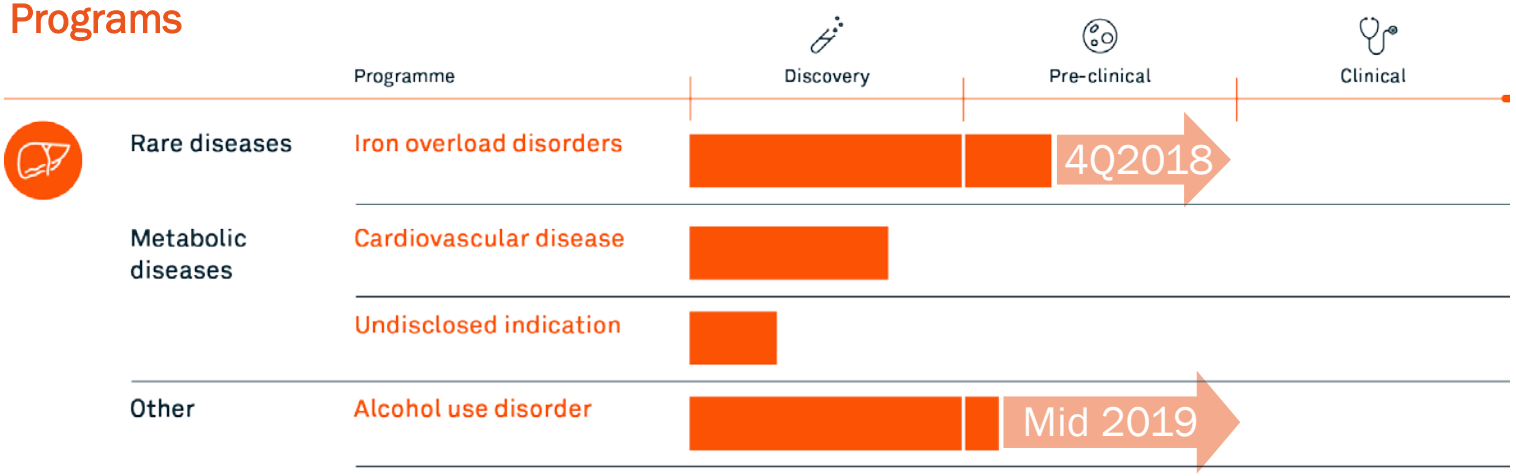
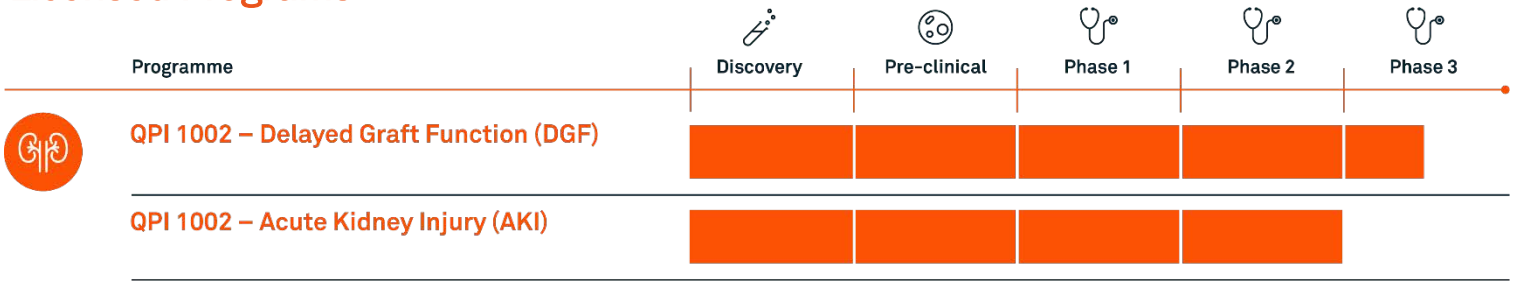
Pipeline

Building a proprietary portfolio, two projects advanced into preclinical development

Our Programs



Out-Licensed Programs



Quark

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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,
Head of Corporate Development.



Michael Mulqueen,
Head of BD & Licensing



Alison Gallafent,
Head of Intellectual Property.



Ulrich Zugel,
Head of Pre-Clinical Drug Discovery.



Linnea Elrington,
Head of Human Resources.

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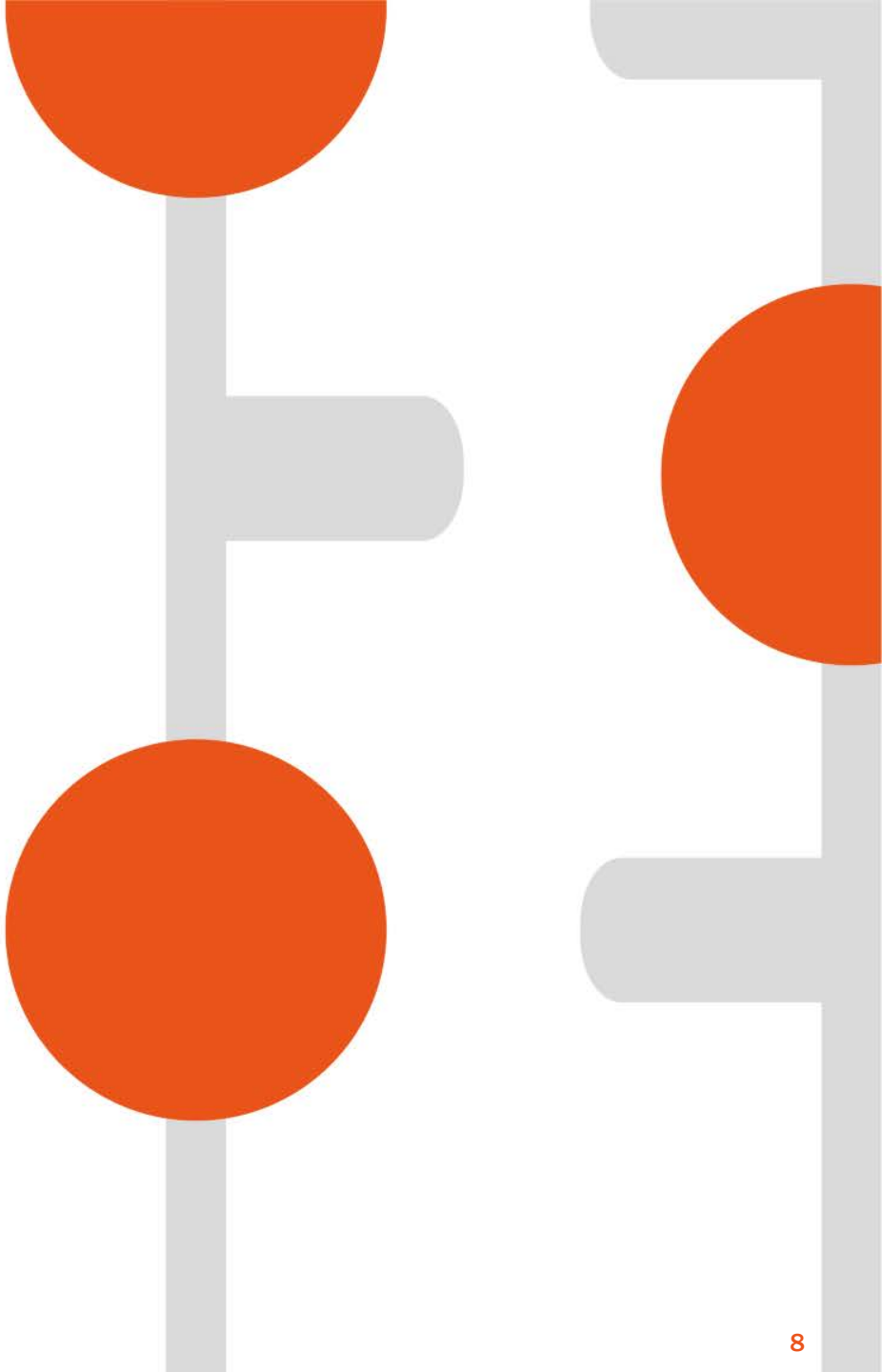
GalNAc-siRNA Platform Technology



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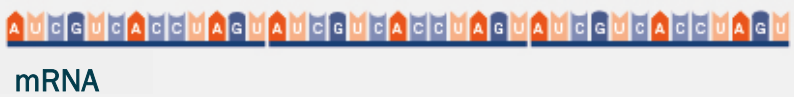
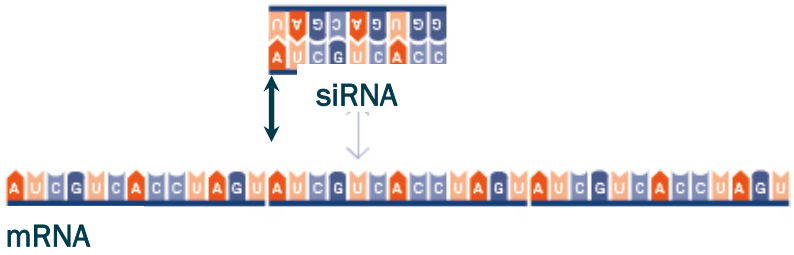
siRNA Mechanism Of Action

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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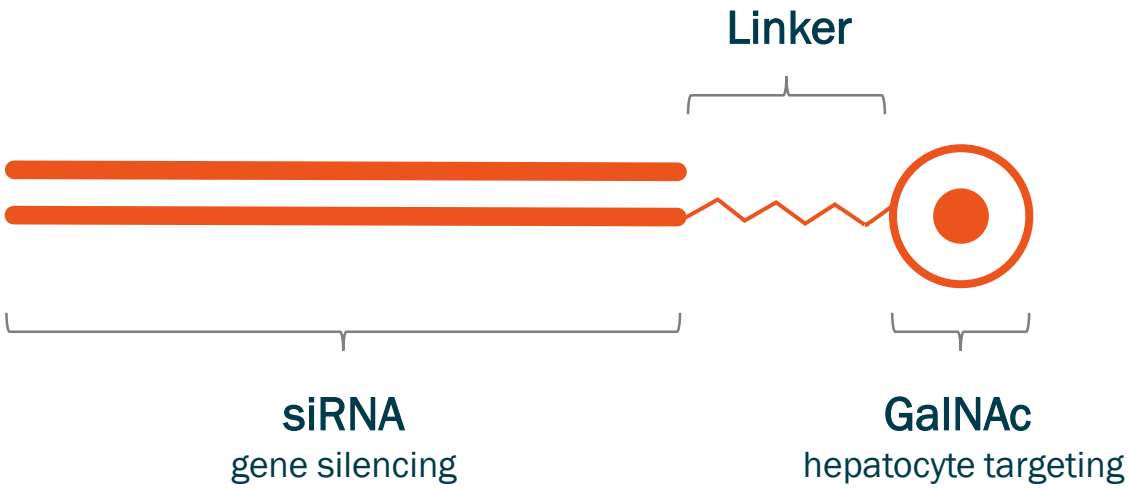
GalNAc-siRNA molecules



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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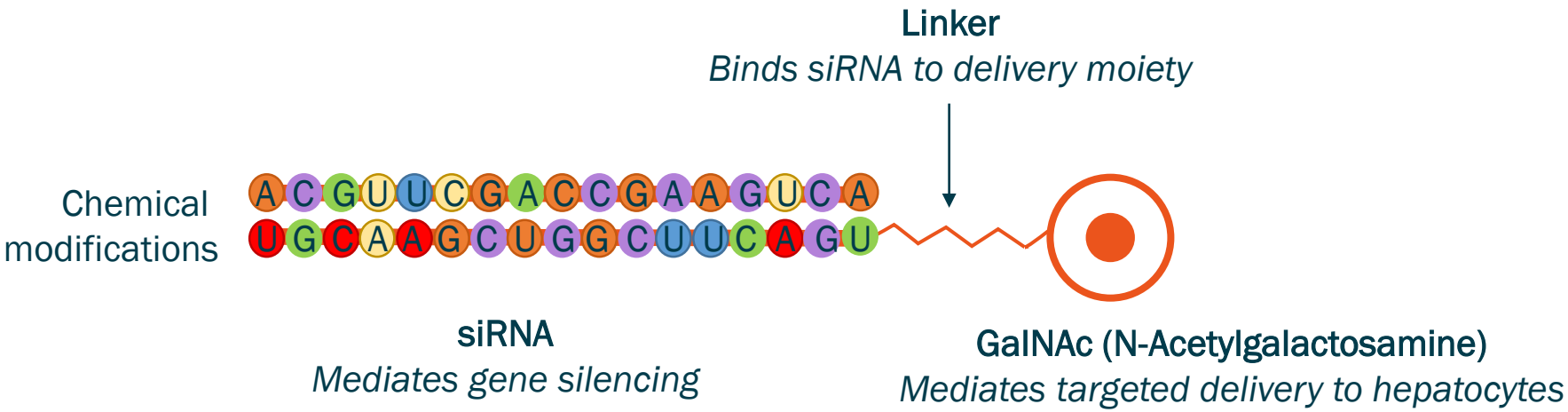
GalNAc-siRNA medicines

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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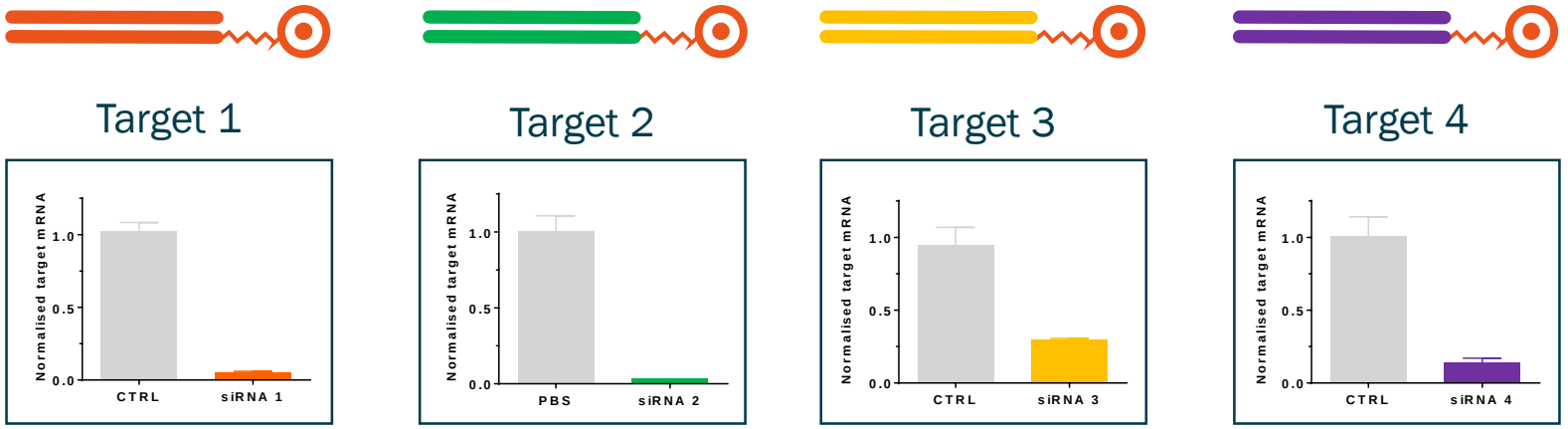
Platform performance

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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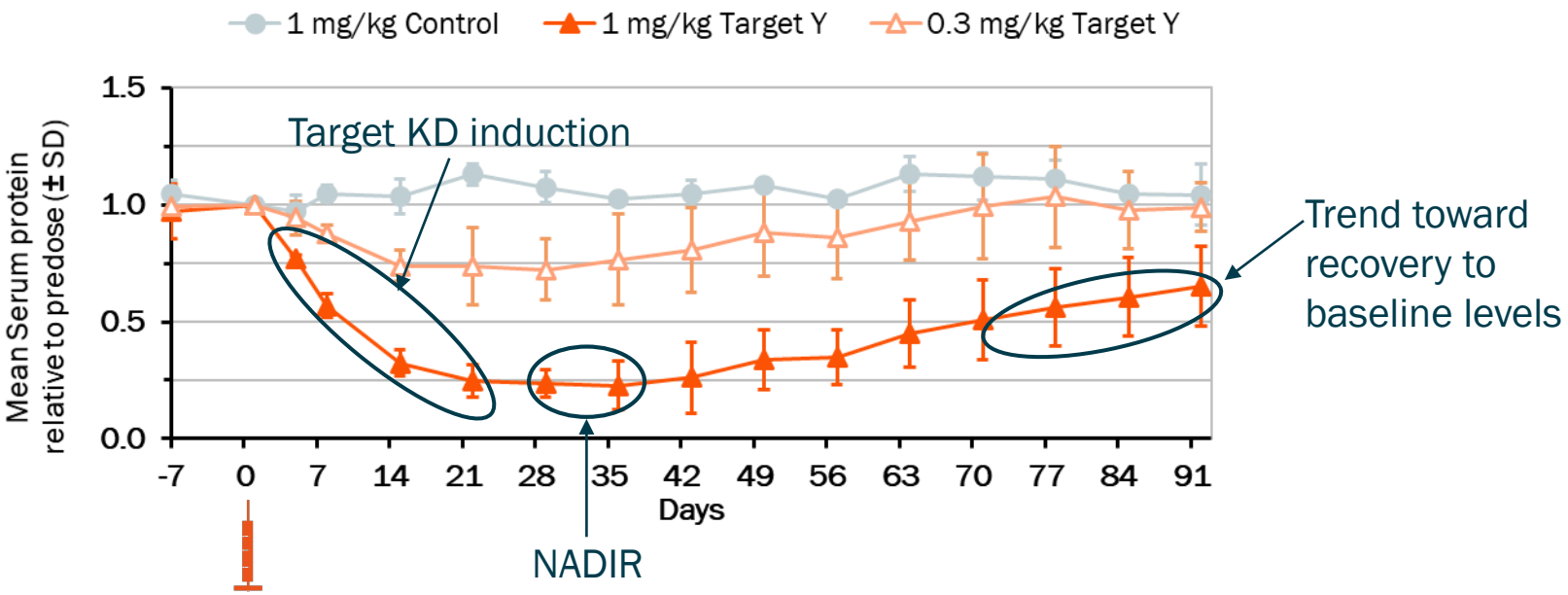
Advantageous properties of our medicines

- > 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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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 need licenses 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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Milestones for the next 12 months



- File Iron Overload CTA Q4 2018
- Secure validating Pharma deal in 2018 utilizing our GalNAc platform technology
- Progress existing pipeline, including potential out-license inflexion points
- Add new targets to pipeline, and utilize next generation molecules
- Continue defensive UK litigation action
- Add further Development expertise to the senior team as pipeline progresses

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Summary

LEADING RNA INTERFERENCE PLATFORM

- Platform being leveraged to build and progress a therapeutic pipeline
- Accelerating pre-clinical discovery, targeting genes in the liver with high specificity
- Modular process is readily reproducible
- Big Pharma is displaying renewed interest in accessing RNAi as part of a broader investment in genetic medicines

SILENCE OWNS FOUNDATIONAL, VALIDATED IP

- Essential for the clinical and commercial viability of the field
- External party licensing validates importance
- Future licensing agreements planned under broad foundational technology and more recent patent filings

STRONG, INTERNATIONAL, SECTOR-EXPERIENCED TEAM

- Track record of proven execution and expertise in RNAi and oligonucleotide fields as well as Pharma and Biotech

LEAD PROGRAM IN IRON OVERLOAD DUE TO FILE IND/CTA IN Q4'18

CASH RUNWAY TO SUPPORT MAJOR MILESTONES - £43.0M ($58.0M) AT 2nd Jan 2018

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APPENDIX

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Board of Directors



Ali Mortazavi

Chief Executive Officer

- Extensive expertise in UK small companies, particularly in biotechnology & technology investments & ventures
- Over 17 years' experience in finance having co-founded Evolution Securities in 2001, heading up the Group's principal trading division
- Joined Silence in 2012, initially as Head of Strategy
- Led the refinancing and refocusing of the business
- International Master of chess and author of numerous books & publications on chess openings and strategies



David Ellam

Chief Financial Officer

- Qualified chartered accountant
- Biotech experience includes several senior finance roles within UK and US publicly owned life science companies
- Previously at BioMarin Pharmaceuticals Inc., Plethora Solutions plc, Ark Therapeutics plc



Alistair Gray

Non-Executive Director

- Wealth of strategic consultancy and business experience
- Trained as an accountant, his early career was in senior management positions with Unilever and John Wood Group PLC
- Previously Director of Arthur Young (now Ernst and Young) Management Consultants and PA Consulting Group for over ten years
- Chaired the Audit and Remuneration committees of AorTech International plc and Highland Distillers plc, as well as the Pension Trustee Board



Dr. Annalisa Jenkins

Non-Executive Chairman

- Over 25 years of global industry experience
- Expertise in advancing programs from scientific research through clinical development
- Prior experience includes CEO of NASDAQ listed Dimension Therapeutics as well as senior leadership positions at Merck Serono and Bristol-Myers Squibb (BMS)
- Began career as a medical officer with the British Royal Navy
- Committee member Science Board to FDA, and serves on various advisory boards



Dr. Stephen Parker

Non-Executive Director

- Over thirty years' experience in the healthcare sector.
- Chairman of Silence Therapeutics from 2015-2017
- Previously Partner with Celtic Pharma funds, Chief Financial Officer of Oxford GlycoSciences plc and a senior investment banker with Barings, Warburg' and Apax Partners



Dr. Andy Richards CBE

Non-Executive Director

- Established track record in founding and scaling up innovative Biotech and Healthtech companies in the UK
- Early career spanned positions with ICI (now AstraZeneca) and PA Technology, and founder and executive director of Chiroscience plc
- Since 1999 he has founded, invested in and helped to scale more than 25 innovative ventures including Vectura, Arakis, Cambridge Biotechnology Ltd and Geneservice
- Andy is a founder member of the Cambridge Angels and a trustee of the British Science Association

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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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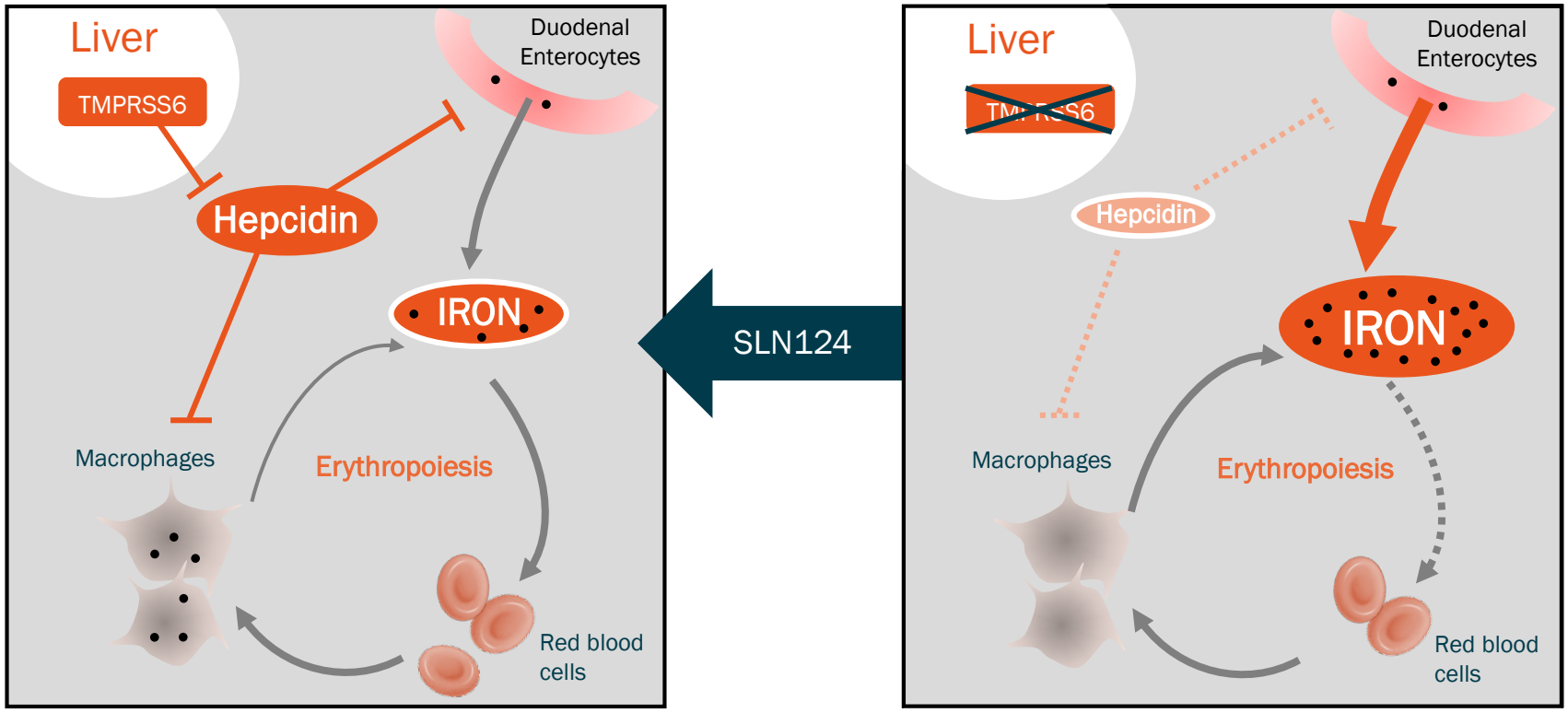
TMPRSS6 is a negative regulator of hepcidin and plays a key role in iron homeostasis

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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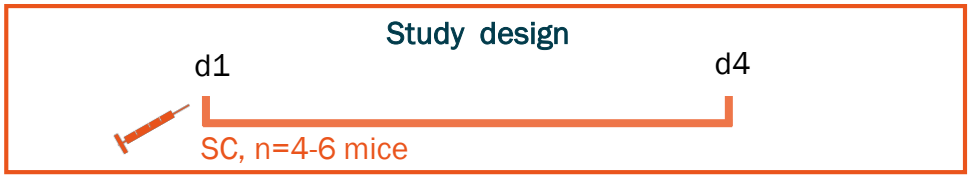
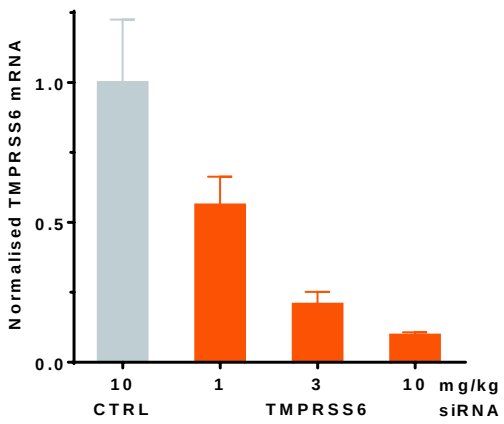
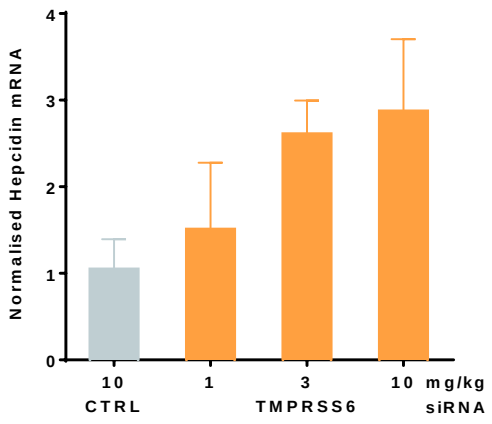
Silencing TMPRSS6 lowers serum iron levels in mice



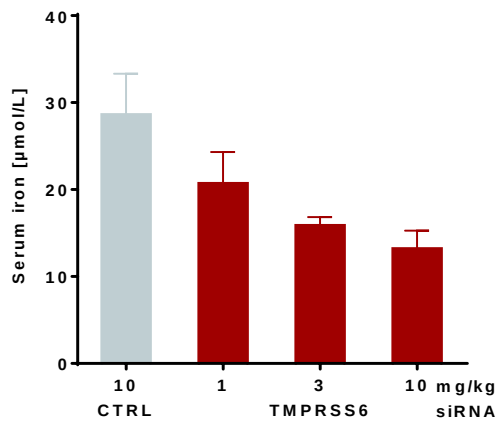
TMPRSS6 mRNA (liver)



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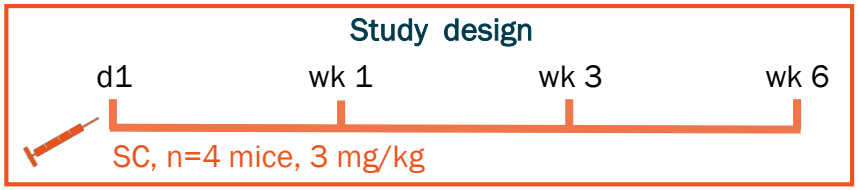
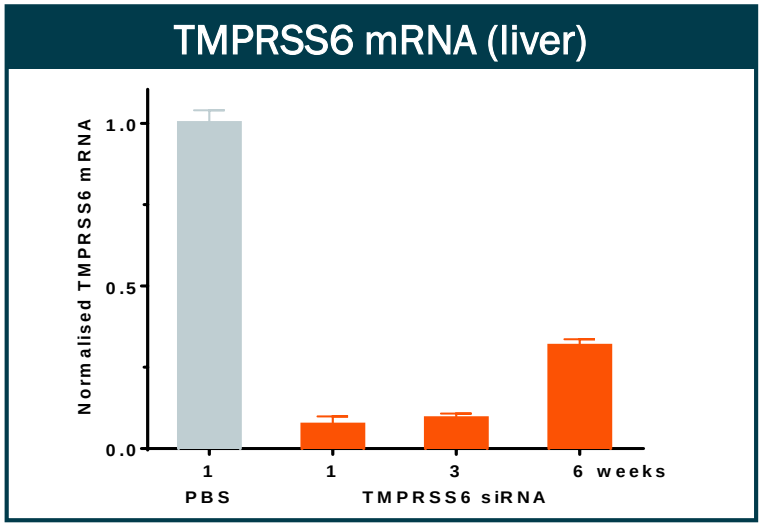
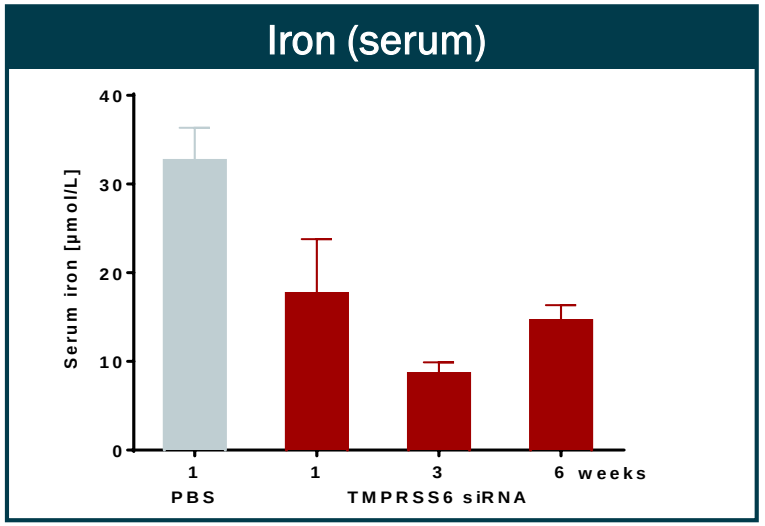
SLN124 lowers iron levels for at least 6 weeks after single administration in mice







> 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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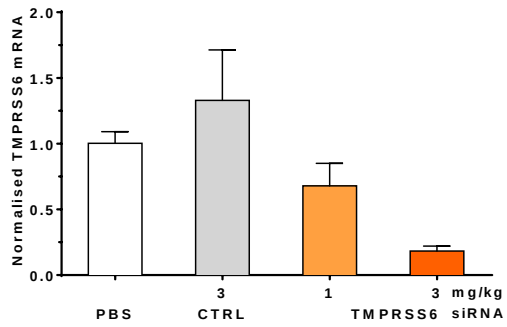
DISEASE MODEL: Therapeutic activity of SLN124 in an iron overload model (HFE -/- mice) - 1/2

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

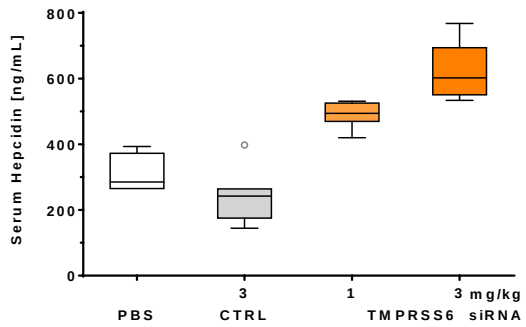
Study design



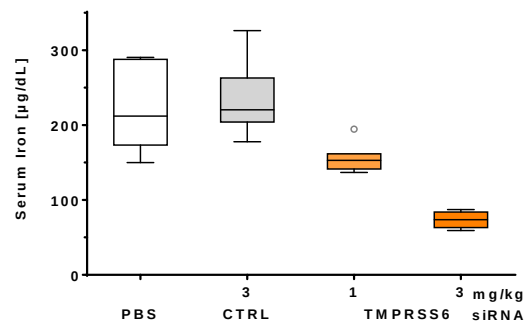
TMPRSS6 mRNA (liver)



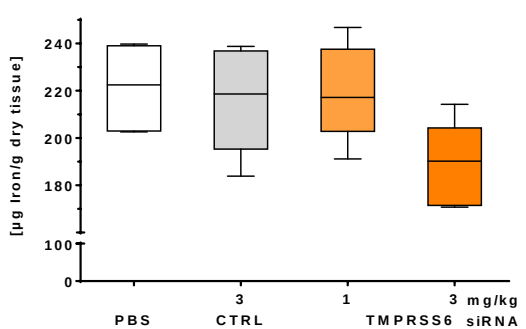
Hepcidin (serum)



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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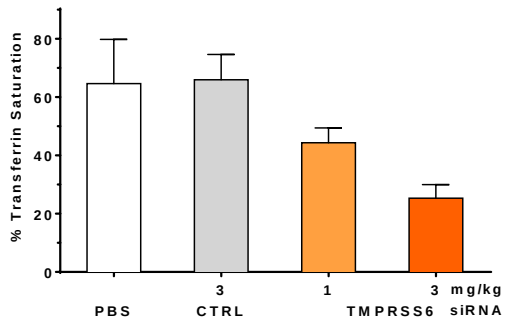
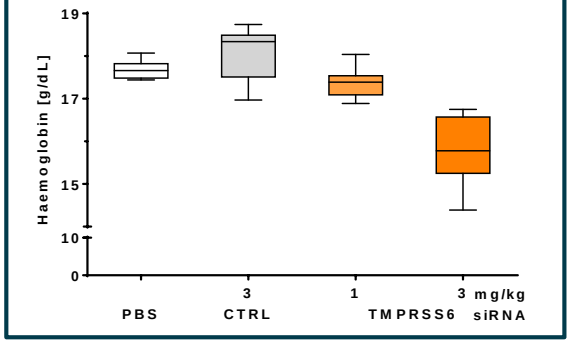
DISEASE MODEL: Therapeutic activity of SLN124 in an iron overload model (HFE -/- mice) - 2/2

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

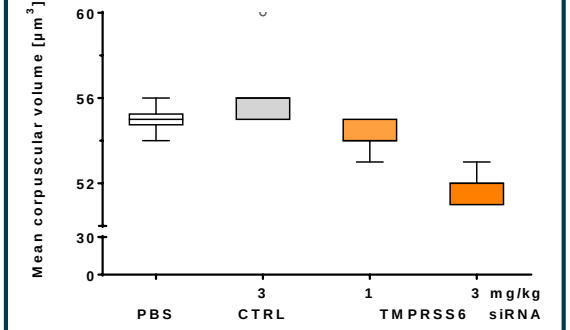
Transferrin Saturation



Haemoglobin



Mean corpuscular volume



> Reversion of transferrin saturation to physiological values

> Normalization of haematological parameters

> Therapeutically active in HFE -/- mice after single administration

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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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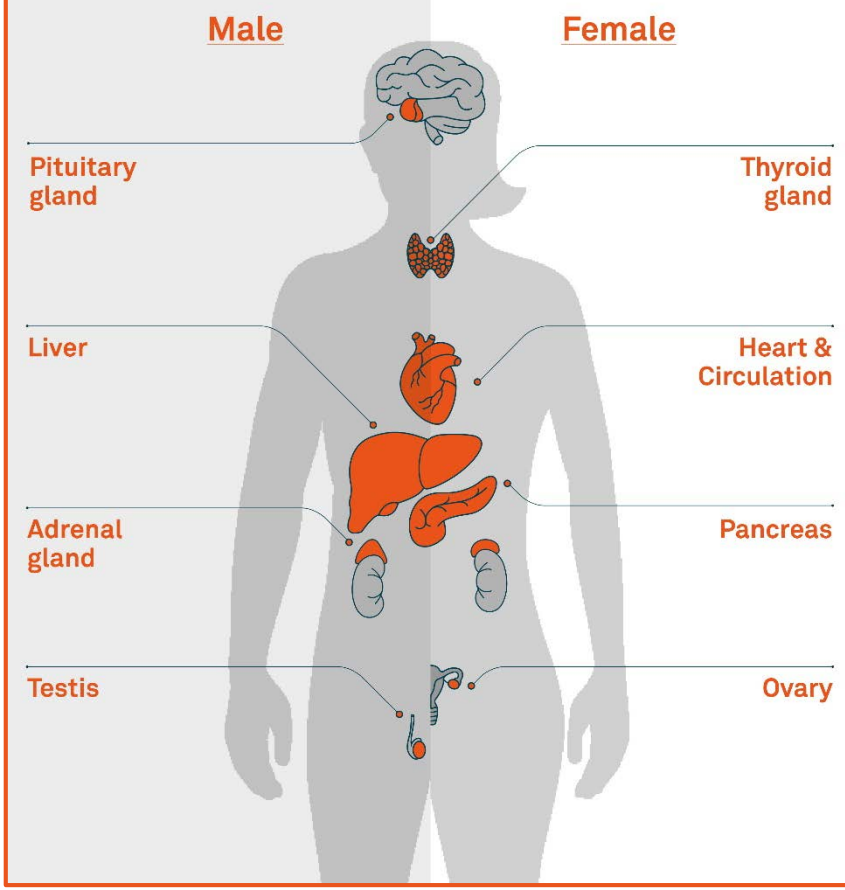
Iron Overload Disorders

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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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

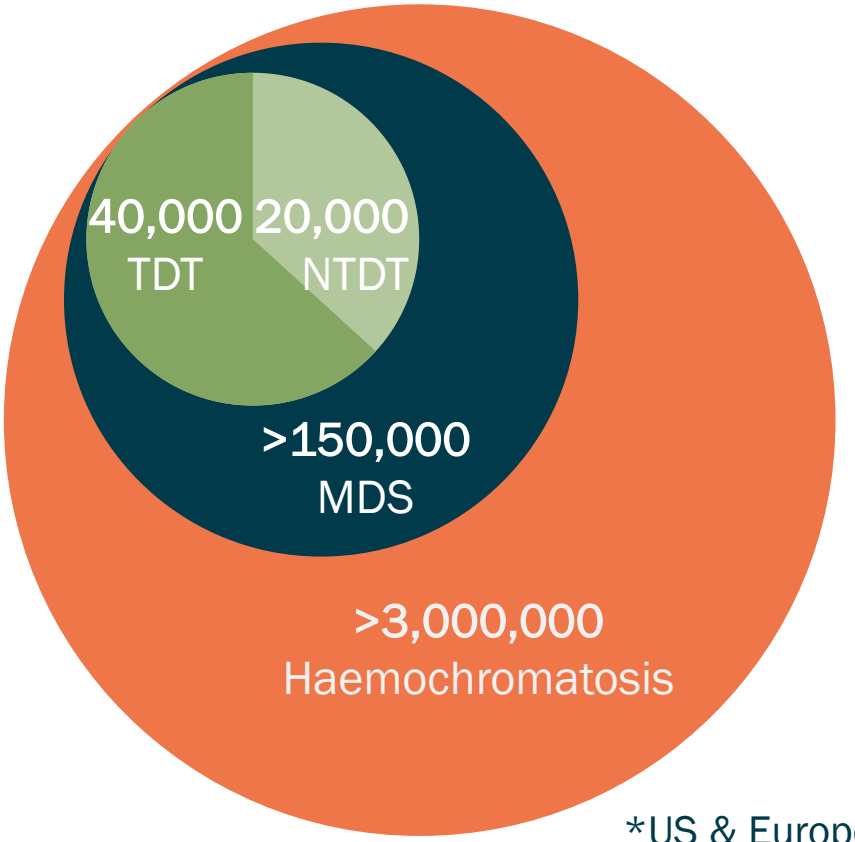
β-Thalassemia intermedia (NTDT)

- 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 - 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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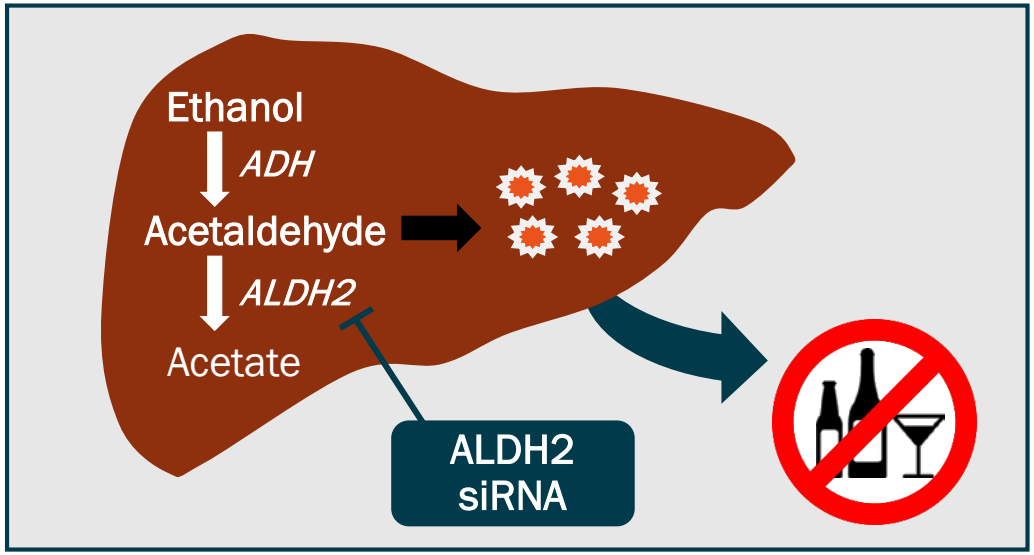
SLN226 mechanism of action

- 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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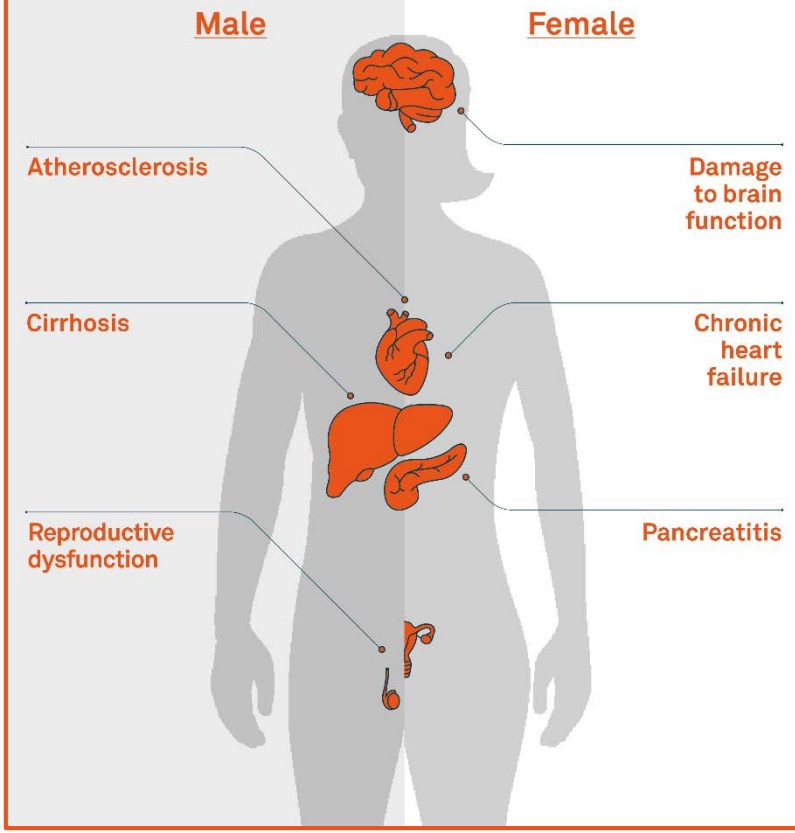
Alcohol use disorder facts

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

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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Market opportunity of SLN226 (US & Europe)



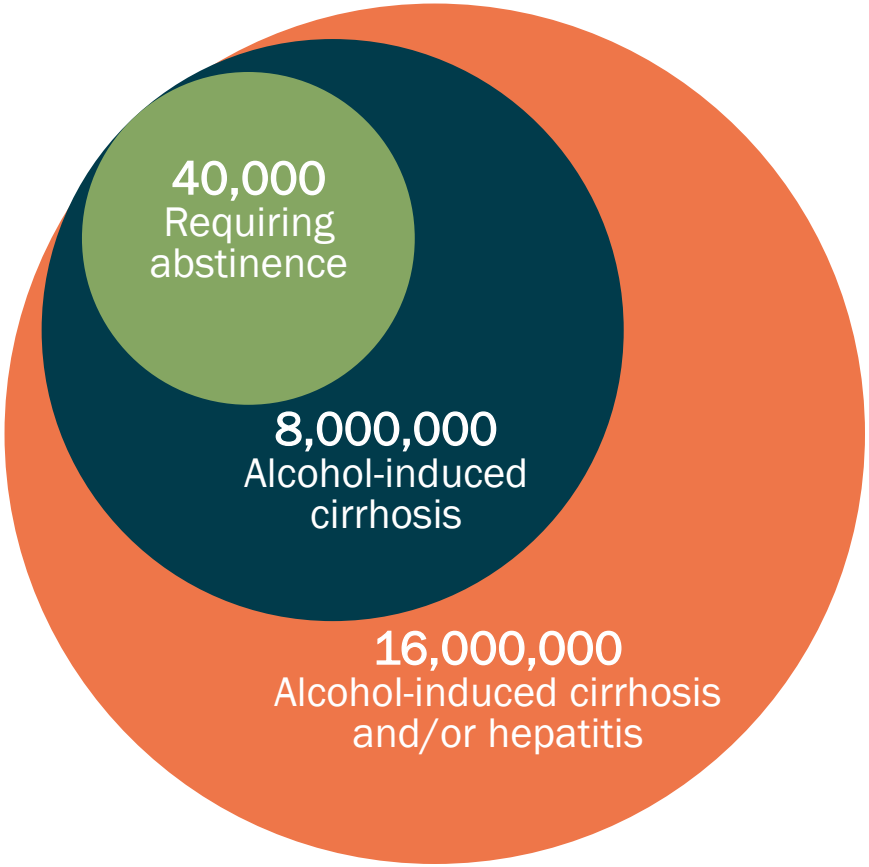
Patients urgently requiring abstinence

- 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
- 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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