SILENCE THERAPEUTICS

Cowen Healthcare presentation March 13th 2018

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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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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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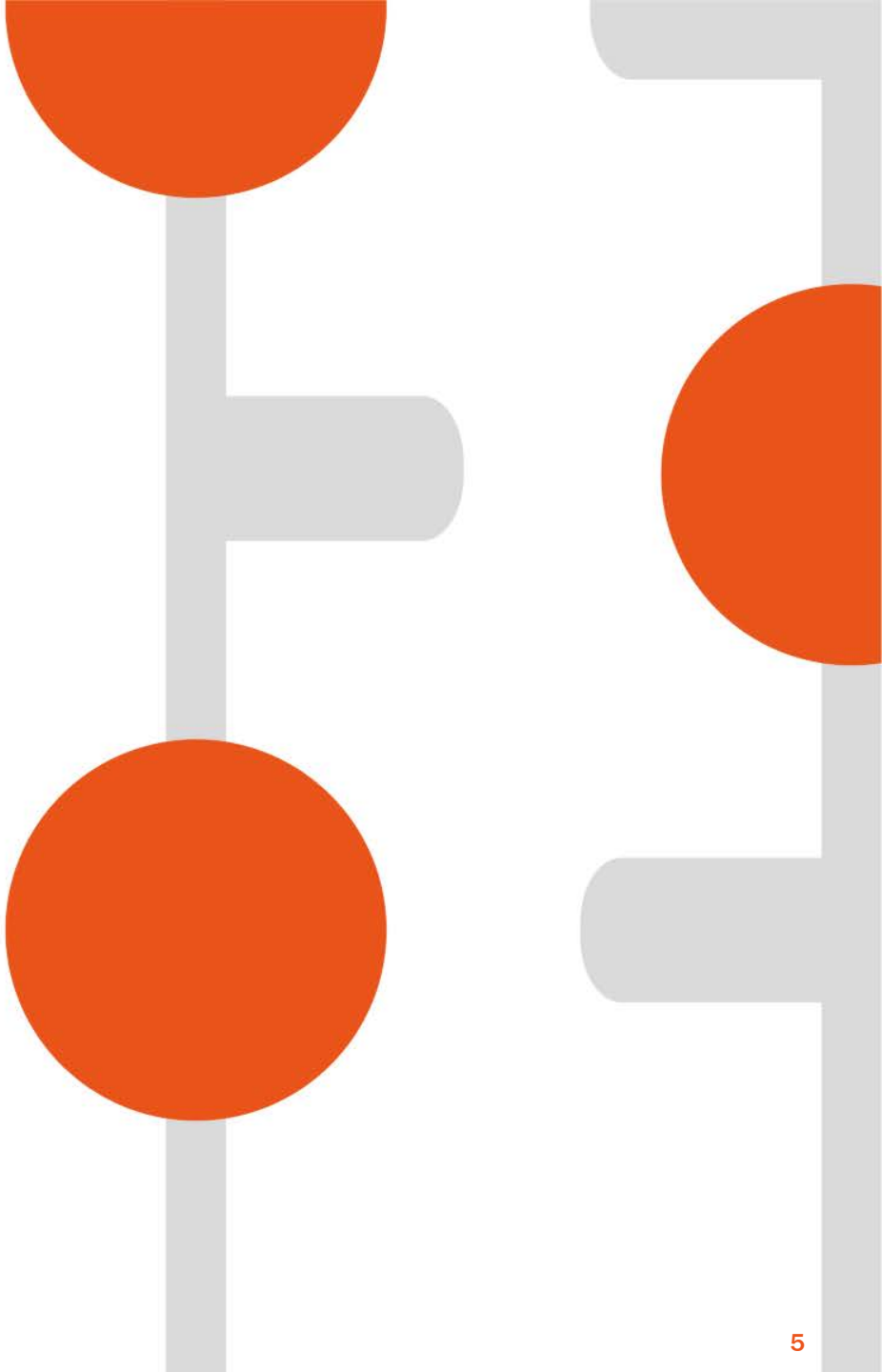
GalNAc-siRNA Platform Technology



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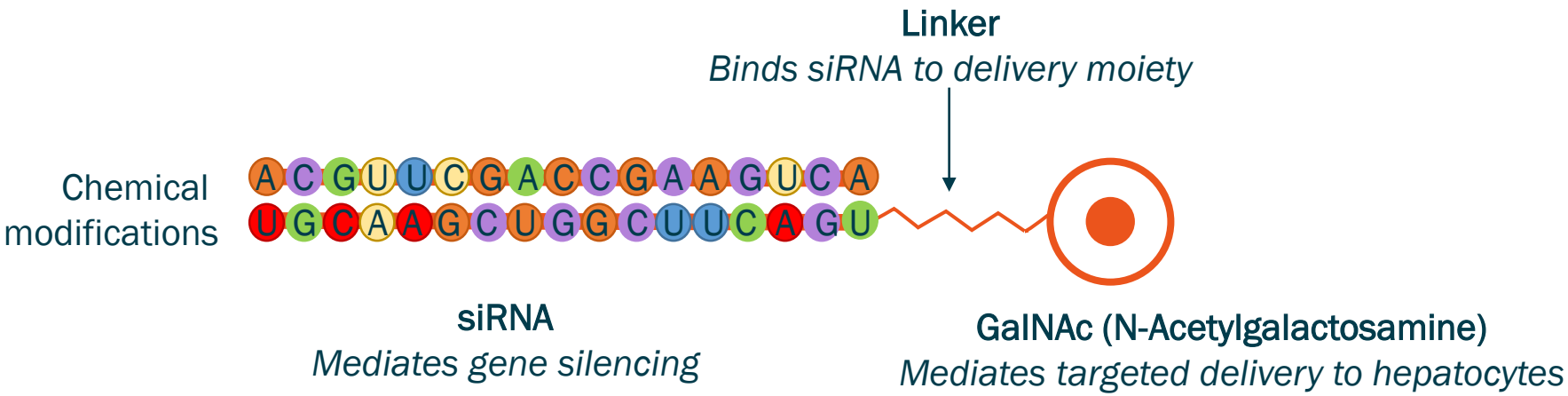
GalNAc-siRNA Medicines

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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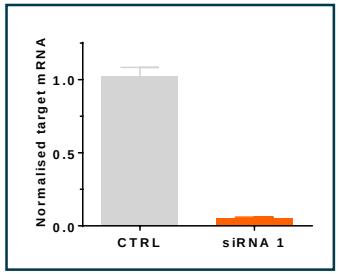
Platform Performance

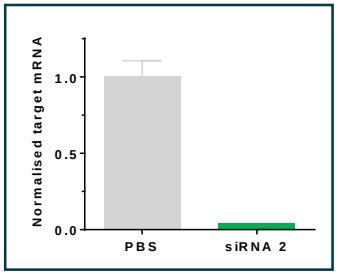
Platform technology: GalNAc-siRNA, able to mediate highly specific gene silencing in hepatocytes (liver) – "Specificity upon specificity"

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

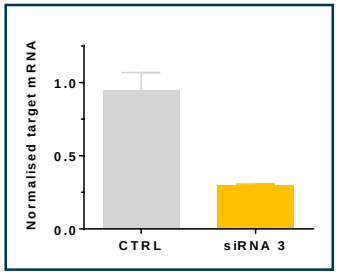
Target 1



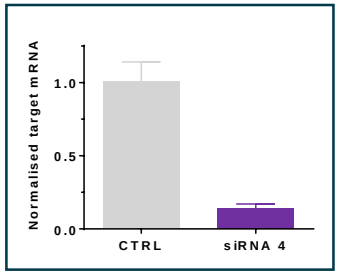
Target 2



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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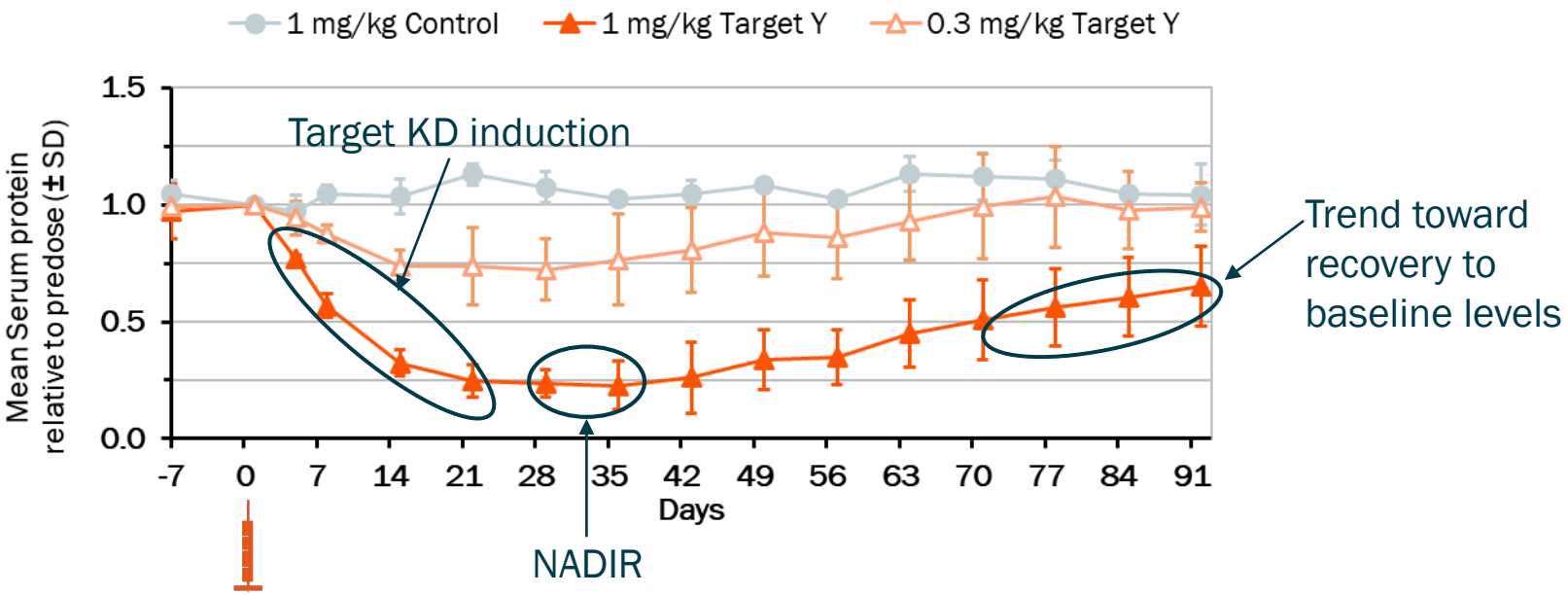
Advantageous Properties of Medicines

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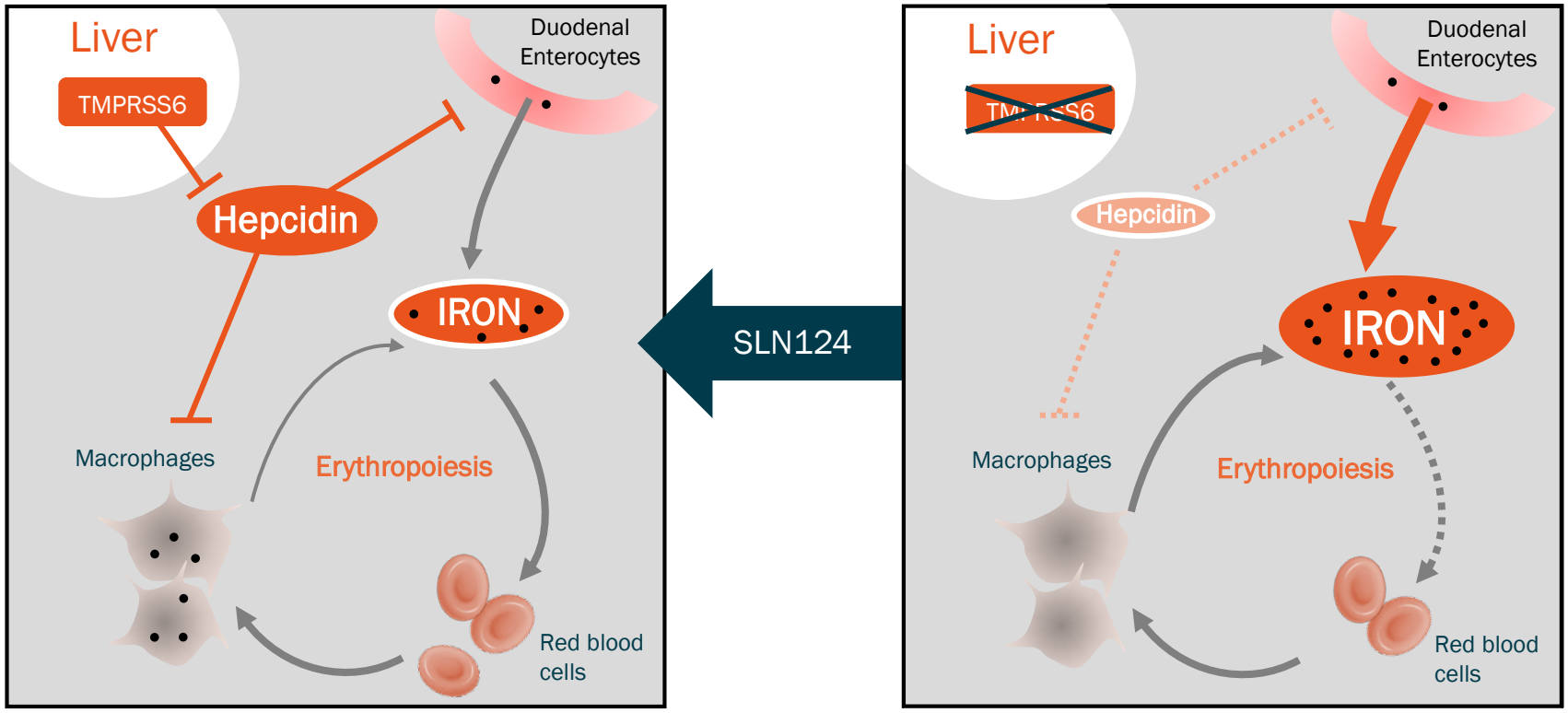
TMPRSS6 is a Negative Regulator of Hepcidin and Plays a Key Role in Iron Homeostasis

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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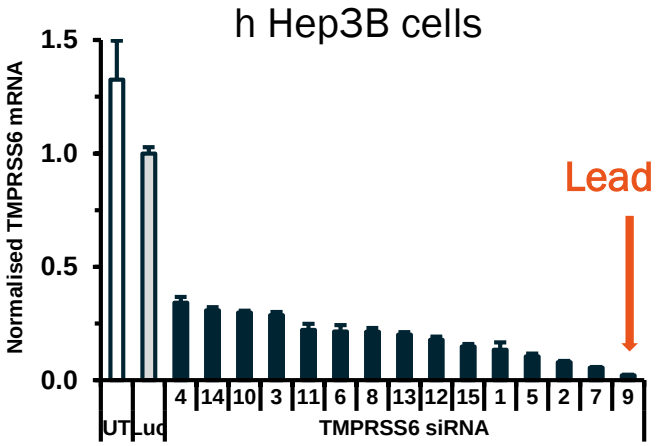
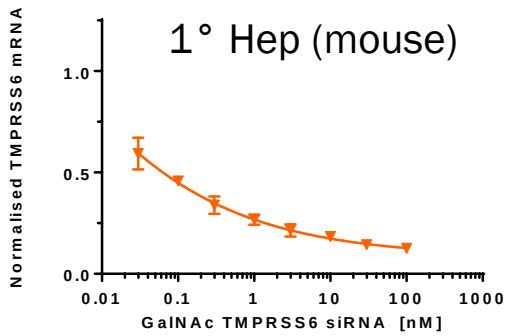
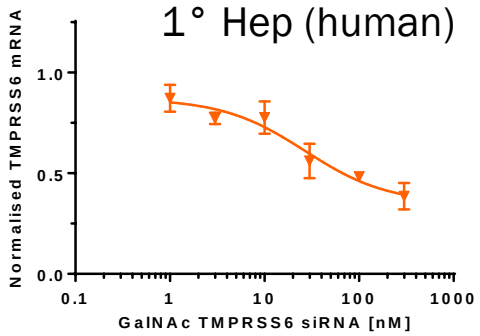
siRNA Screen and GalNAc Conjugate Testing in Primary Hepatocytes

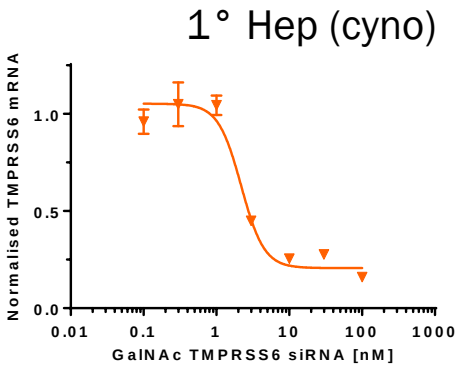
TMPRSS6 mRNA
(in vitro screen – Selected siRNAs)



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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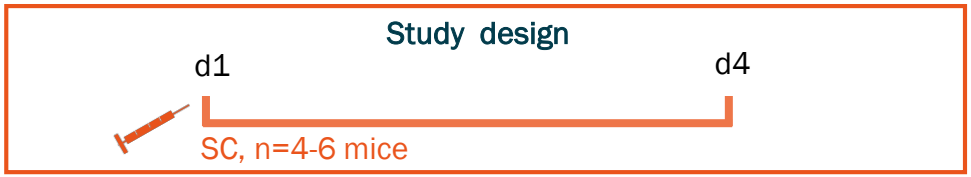
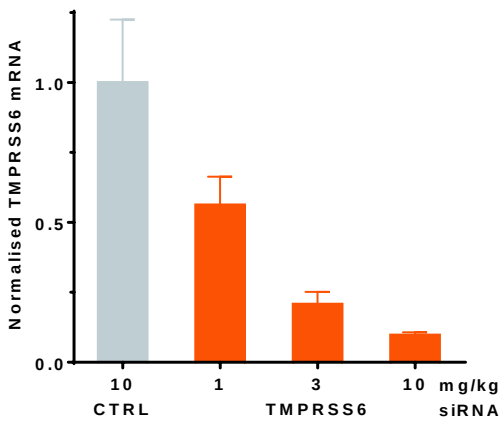
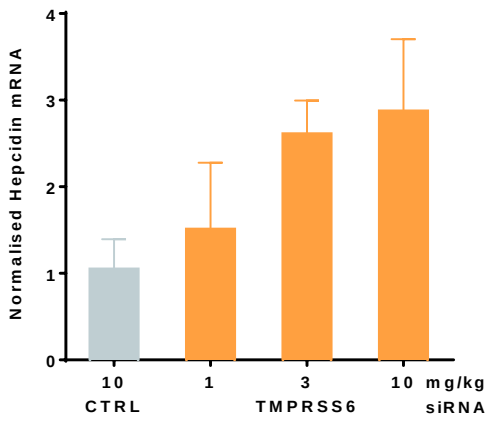
Silencing TMPRSS6 Lowers Serum Iron Levels in Mice



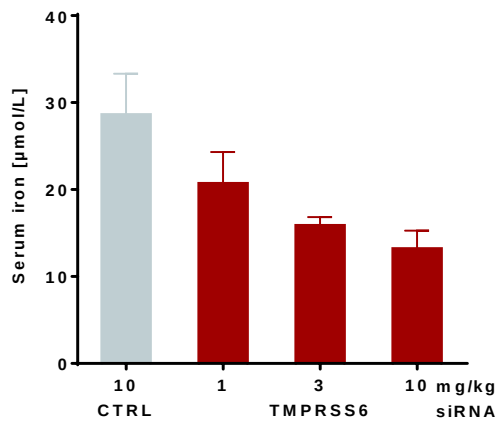
TMPRSS6 mRNA (liver)



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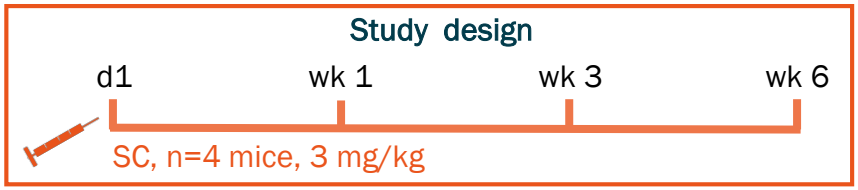
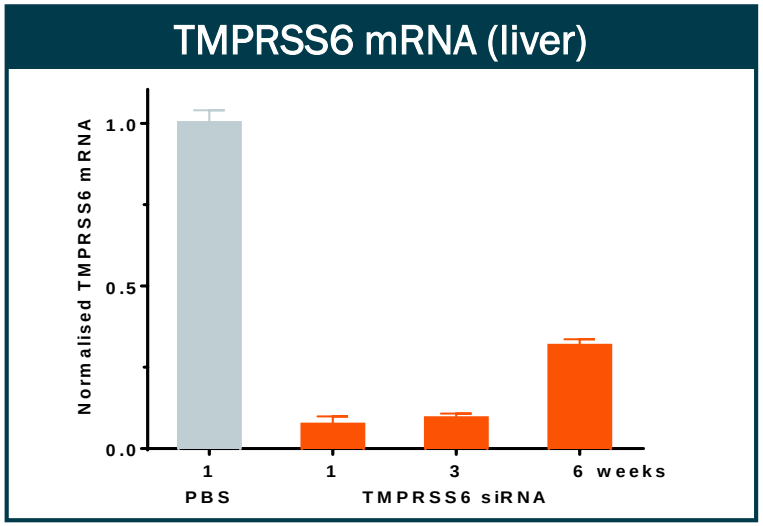
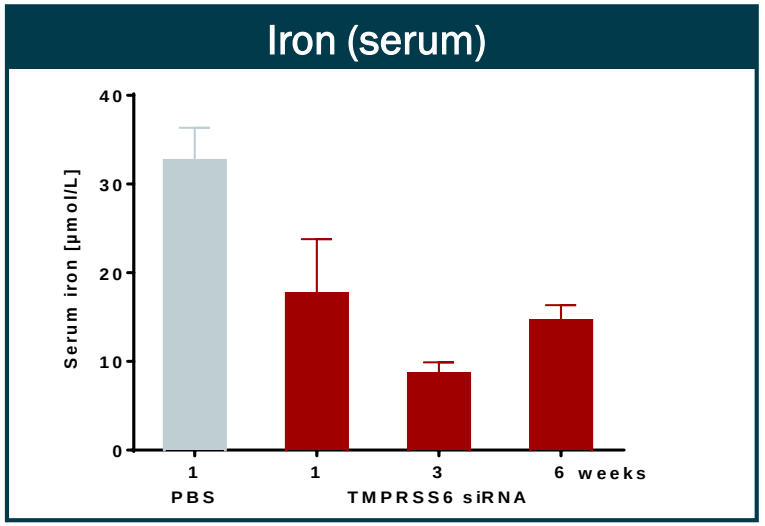
SLN124 Lowers Iron Levels for at Least 6 Weeks After Single Administration in Mice







> 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)

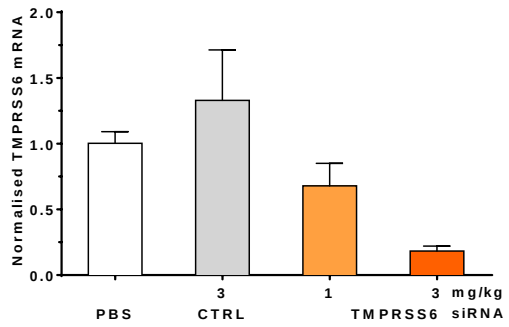
Collaboration with
Prof. Dr. Martina Muckenthaler
University of Heidelberg, Germany

Study design

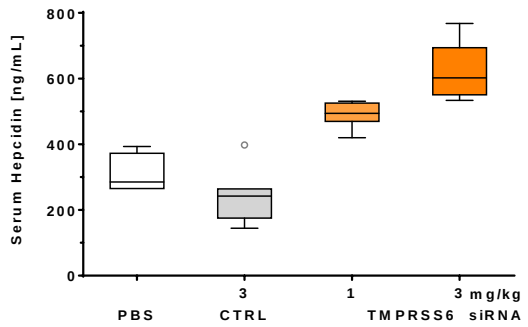
d1 — wk 3

SC, n=6-7 mice

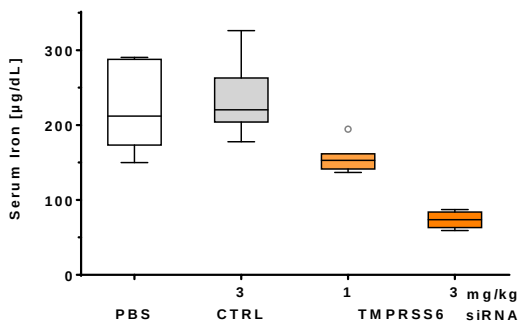
TMPRSS6 mRNA (liver)



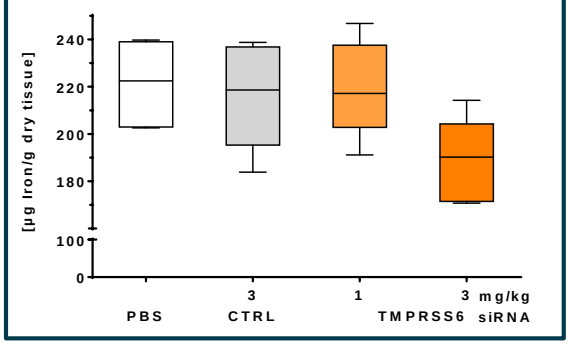
Hepcidin (serum)



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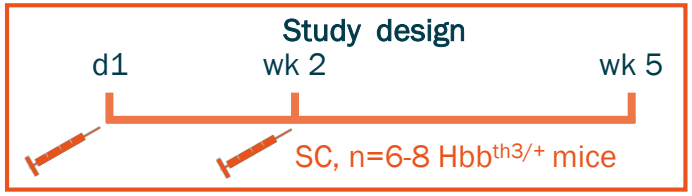
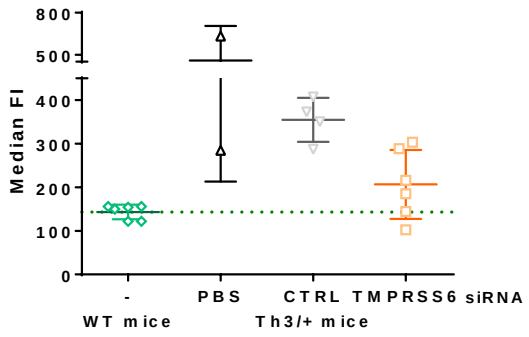
SLN124 Normalises ROS Species & Improves RBC Parameters in β-Thalassemia Disease Model

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

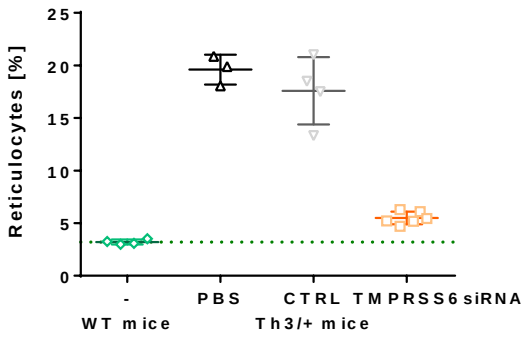
HUDSON INSTITUTE OF MEDICAL RESEARCH



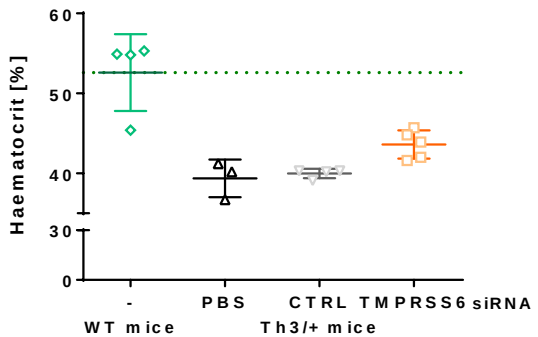
Reactive oxygen species (ROS)



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

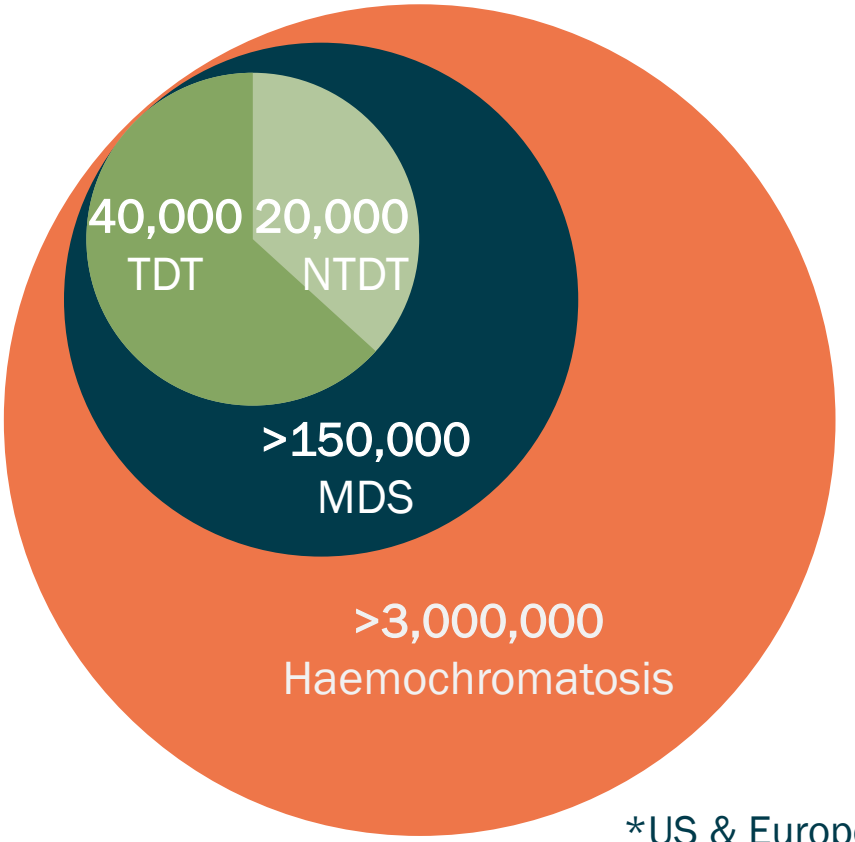
β-Thalassemia intermedia (NTDT)

- 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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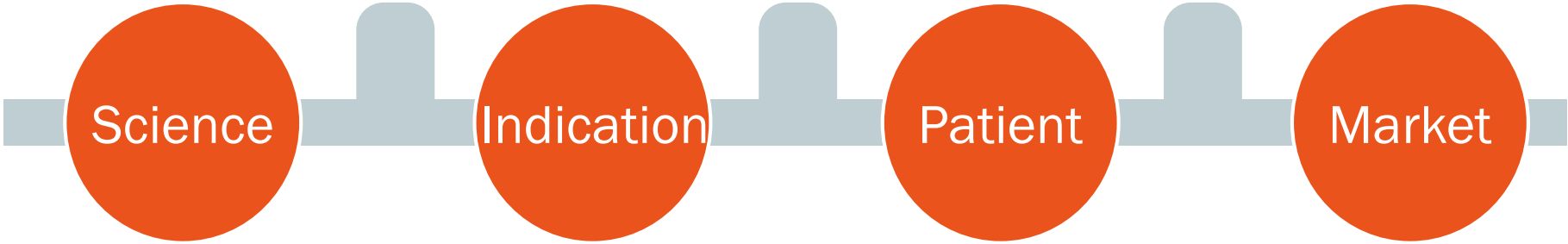
Why we are Excited about SLN124?



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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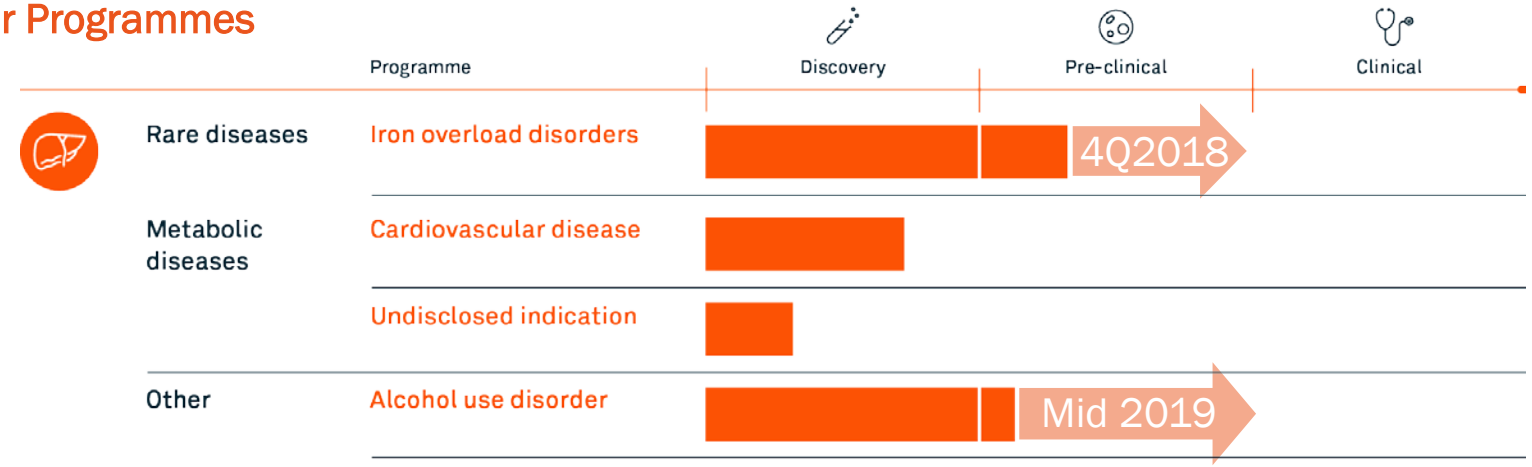
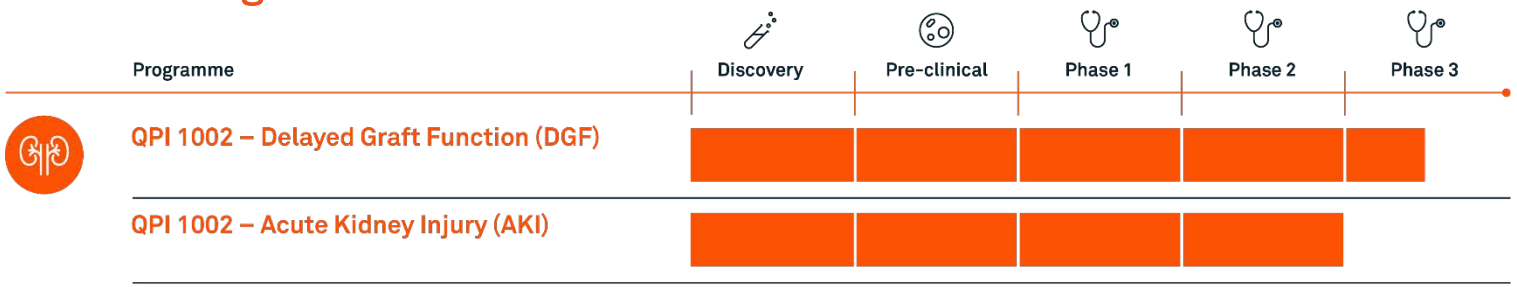
Pipeline - Building a Proprietary Portfolio

Internal programmes advanced into preclinical development

Our Programmes



Out-Licensed Programmes



Quark

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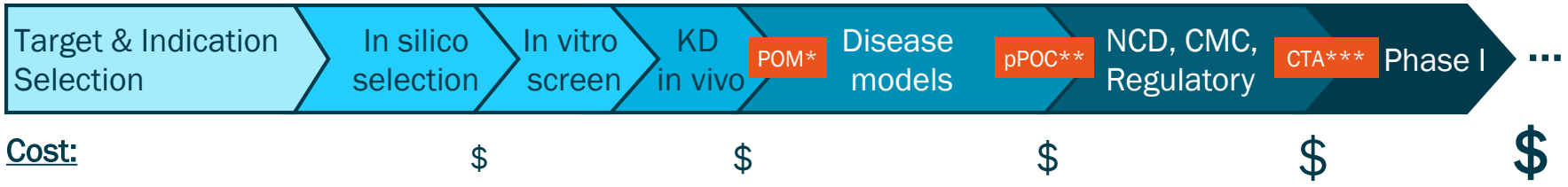
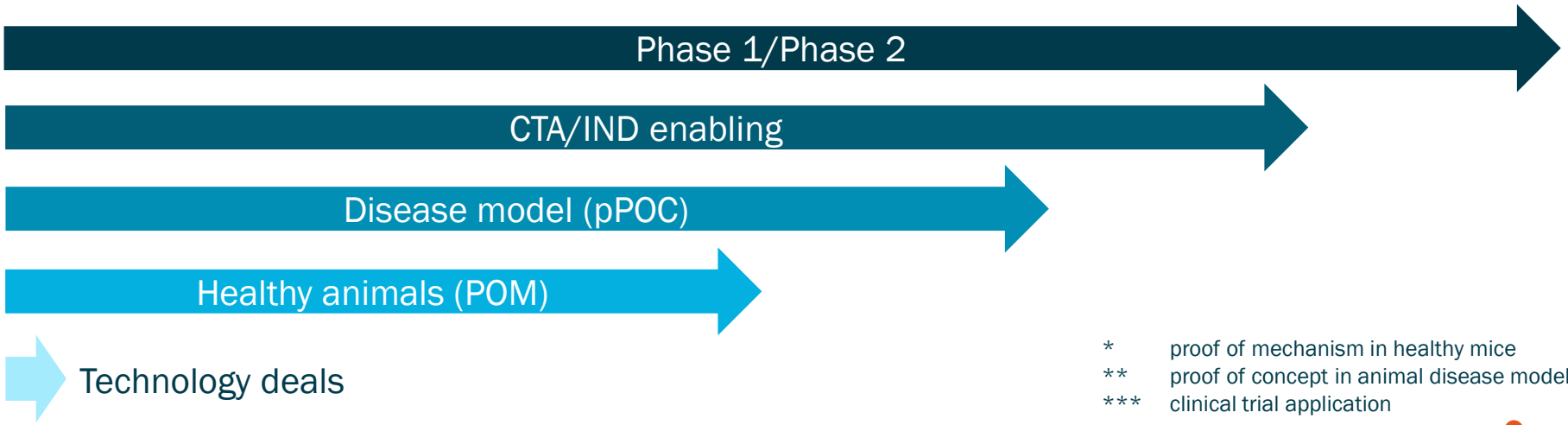
Platform Strategy

~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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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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