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

Ali Mortazavi, Ph.D.
Chief Executive Officer
Since 2012

Dmitry Samarsky, Ph.D.
Chief Scientific Officer
Since 2016

Laura Roca-Alonso, Ph.D.
Head of Corporate Development
Since 2014

Ulrich Zugel, Ph.D.
Head of Pre-Clinical Drug Discovery
Since 2016

Alison Gallafent
Head of Intellectual Property
Since 2017

Linnea Elrington
Head of Human Resources
Since 2017

Torsten Hoffmann, Ph.D.
Chief Operating Officer
Since 2017

David Ellam, Ph.D.
Chief Financial Officer
Since 2016

Michael Mulqueen
Head of BD & Licensing
Since 2017

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GalNAc-siRNA Platform Technology
Schematic structure of our therapeutic molecules:

- **siRNA**: Mediates gene silencing
- **GalNAc** (N-Acetylgalactosamine): Mediates targeted delivery to hepatocytes
- **Linker**: Binds siRNA to delivery moiety

**Chemical modifications**:

```
ACGUUCGACCGGAAGUCAC
UGCAAGCGUGGCUCAGU
```

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

1. GalNAc as a targeting ligand per se is free to use
2. We have a robust position for our foundational chemical modification technology
3. We patent our linker chemistries
4. We patent our potent and highly specific siRNA constructs and lead sequences
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.
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

![Graph showing mean serum protein relative to predose (±SD) over time.](image)

- Target KD induction
- Trend toward recovery to baseline levels
- NADIR
SLN124 for the treatment of Iron Overload Disorders

A case study of our platform
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
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

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TMPRSS6 = Transmembrane Protease, Serine 6
Lead siRNA for TMPRSS6 identified (picomolar IC50 by transfection)

GalNAc-siRNA conjugate is functional in primary hepatocytes from different species (mouse, human, cynomolgus)
Silencing TMPRSS6 Lowers Serum Iron Levels in Mice

> Single subcutaneous administration results in specific KD of TMPRSS6
> Upregulated Hepcidin causes reduction of blood iron levels
> Proof of mechanism demonstrated
SLN124 Lowers Iron Levels for at Least 6 Weeks After Single Administration in Mice

Study design
- d1
- wk 1
- wk 3
- wk 6
- SC, n=4 mice, 3 mg/kg

<table>
<thead>
<tr>
<th>Study design</th>
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<tbody>
<tr>
<td>d1</td>
<td>wk 1</td>
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<td>wk 3</td>
<td>wk 6</td>
</tr>
<tr>
<td>SC, n=4 mice</td>
<td>3 mg/kg</td>
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</tbody>
</table>

**TMPRSS6 mRNA (liver)**

- PBS
- TMPRSS6 siRNA

**Iron (serum)**

- PBS
- TMPRSS6 siRNA

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

> 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

**Study design**
- d1
- wk 3
- SC, n=6-7 mice

**Collaboration with**
Prof. Dr. Martina Muckenthaler
University of Heidelberg, Germany
SLN124 Normalises ROS Species & Improves RBC Parameters in β-Thalassemia Disease Model

> 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
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
**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**

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

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

*US & Europe*
Why we are Excited about SLN124?

**Science**
- **What does the Mode of action bring?**
  - **2018:** Gene silencing via siRNA is a proven concept
  - SLN124 has proven to increase hepcidin and **reduce iron plasma levels**, thus restoring iron homeostasis
  - The GalNAc conjugate **targets hepatocytes** in the liver, acting specifically at hepcidin’s predominant synthesis site
  - SLN124 is **highly specific** targeting a single gene

**Indication**
- **How does the science connect to the diseases?**
  - **beta-Thalassemia**
  - **Myelodysplastic Syndromes**
  - **Potential for Haemochromatosis**
  - **Central role of hepcidin enables lowering of iron plasma levels**, **optimising erythropoiesis**
  - **Mechanistic claim** – treatment of iron overload disorders

**Patient**
- **What is the patient benefit?**
  - SLN124 has the potential to become an **essential component of the future SoC**
  - **QoL parameters** will be improved **such as transfusion frequency and drug burden of chelators**
  - Enables an early treatment option for the **prevention of iron deposition in organs**
  - **Pediatrics and adults will be treated**
  - We will work with patient organisations in 2018

**Market**
- **When and where do we want to market it?**
  - **First In Class** in iron overload
  - **High value product** with peak sales of $600 million (BT) and $3 billion (MDS)
  - **Launch** would be expected by 2024/25 via an Orphan designation
  - A corporate strategy is required to access geographies in the **middle and far east**
  - We are seeking **commercialisation partnerships**
Internal programmes advanced into preclinical development

Our Programmes

<table>
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<tr>
<th>Programme</th>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>Rare diseases</td>
<td>Iron overload disorders</td>
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<tr>
<td>Metabolic diseases</td>
<td>Cardiovascular disease</td>
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<td>Undisclosed indication</td>
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<tr>
<td>Other</td>
<td>Alcohol use disorder</td>
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Out-Licensed Programmes

<table>
<thead>
<tr>
<th>Programme</th>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>QPI 1002 – Delayed Graft Function (DGF)</td>
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<tr>
<td>QPI 1002 – Acute Kidney Injury (AKI)</td>
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~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
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