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Silence Therapeutics’ Summary

Valuable Platform
- Reproducible, proprietary gene silencing (RNAi) therapeutics platform, rapidly generating internal pipeline and diversifying out-licensing options

Haematology
- SLN124 (beta-thalassemia & MDS\textsuperscript{1}) to enter the clinic in 2019, with first patient dosed in H2, after promising data in animal models

Strong Experienced Team
- Over 15 years of tenured oligonucleotide R&D expertise; growing clinical team, and experienced biopharma management team

Target Selection
- Focused on targeting indications in rare diseases & large population targets, including new medicine for cardiovascular disease (SLN360)

Strong Financial Position
- $35m of cash\textsuperscript{2} extends runway to key clinical milestones such as interim results from the SLN124 Phase 1b trial.

Notes: 1 MDS = Myelodysplastic syndrome
2 As of 31\textsuperscript{th} Dec 2018 and £=$1.3

HQ in London

R&D in Berlin

Approx. 45 employees across both sites
Recent Highlights

• Clinical Trial Application filed for SLN124 in March 2019 with MHRA
• First patients expected to enter a Phase Ib study in Q3 2019
• Granted Orphan Drug Designation by the European Medicines Agency for the treatment of β-Thalassemia
• SLN360, an Lp(a) targeting siRNA for cardiovascular disease advanced and has started IND-Enabling studies in Feb 2019
• Out-licenced programme, QPI-1002, for Prevention of Acute Kidney Injury progressed to Phase III clinical trial by partner Quark Pharmaceuticals, Inc.
• New leadership in place with the recruitment of Dr David Horn Solomon, an experienced public company biotech CEO and board member as Chief Executive Officer. Dr Giles Campion joins as Head R&D and Chief Medical Officer
• Settlement and License Agreement with Alnylam Pharmaceuticals for tiered royalty on net sales of ONPATTRO™ in the EU
Leadership

CEO

David Horn Solomon

➢ Experienced public company CEO, board member and biotech investor
➢ CEO of Zealand Pharma from 2008 to 2015, during which time the company went public on Nasdaq OMX and and its lead product, Adlixin® was approved in the US
➢ Previously Faculty Columbia University and founder Carrot Capital Healthcare Ventures

Head R&D, CMO

Giles Campion

➢ Former Chief Medical Officer and SVP R&D at Prosensa (2009-2016), playing a major role in their Nasdaq IPO and subsequent sale to Biomarin for $680m
➢ Most recently CMO at Albumedix
➢ Spent 5 years in senior R&D roles at Novartis
➢ Medical degree from Bristol University

CFO

Rob Quinn

➢ Chartered accountancy training at Deloitte before joining GSK
➢ Area Finance Director for Africa and Developing Countries at GSK (responsible for >£400m revenue)
➢ Joined Silence in early 2017 as Head FP&A
➢ PhD in Biochemistry from the University of Manchester
Reproducibly silencing disease-associated genes using our proprietary platform technology

Platform technology with freedom to operate: GalNAc-siRNA, able to mediate highly specific gene silencing in hepatocytes (liver) – “Specificity upon specificity”

Patient friendly: Subcutaneous delivery and infrequent dosing (monthly or longer). Well tolerated.

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

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<td>Undisclosed indication</td>
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<td>Cardiovascular diseases</td>
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<td>SLN360</td>
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<tr>
<td>Cardiovascular disease</td>
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<td>IND/CTA planned for H2 2020</td>
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<td>Rare diseases</td>
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<td>Complement-mediated diseases</td>
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<td>Rare metabolic</td>
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<td>Rare undisclosed</td>
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Out-Licensed Technology to Quark Pharmaceuticals

- **QPI 1002 – Delayed Graft Function (DGF)**
- **QPI 1002 – Acute Kidney Injury (AKI)**
SLN124
for the treatment of
Iron Overload Disorders
Market Opportunity of SLN124

US and EU patients

\[ \beta \text{-Thalassemia} \]
~40,000 TDT\(^1\)
~20,000 NTDT\(^2\)

MDS\(^3\)
>100,000

Benefits of SLN124

SLN124 aims to:
1. Reduce organ iron levels &
2. Enhance erythropoiesis

Reduced transfusion frequency & Secondary iron overload burden

Notes: 1. TDT = Transfusion Dependent Thalassemia 2. NTDT = Non Transfusion Dependent Thalassemia 3. MDS = Myelodysplastic Syndrome
SLN124 Mechanism of Action: Increasing Hepcidin by Silencing its Repressor TMPRSS6

- **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 anemia & iron overload
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
Therapeutic Activity of SLN124 in a Disease Model of Hereditary Haemochromatosis (HFE\(^{-/-}\) mice)

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

**Study design**
- **d1**
- **wk 3**
- SC, n=6-7 HFE\(^{-/-}\) mice

### TMPRSS6 mRNA (liver)
- **PBS**
- **CTRL**
- **1 mg/kg sIRNA**
- **3 mg/kg sIRNA**
- Normalised TMPRSS6 mRNA
- **p=0.0007**

### Hepcidin (serum)
- **PBS**
- **CTRL**
- **1 mg/kg sIRNA**
- **3 mg/kg sIRNA**
- Serum Hepcidin [ng/mL]
- **p<0.0001**
- **p=0.0042**

### Iron (serum)
- **PBS**
- **CTRL**
- **1 mg/kg sIRNA**
- **3 mg/kg sIRNA**
- Serum Iron [µg/dL]
- **p<0.0001**
- **p=0.0263**

### Iron (kidney)
- **PBS**
- **CTRL**
- **1 mg/kg sIRNA**
- **3 mg/kg sIRNA**
- [µg iron/g dry tissue]
- **p=0.0325**

- **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

© Silence Therapeutics 2019
SLN124 Reduces ROS and Improves RBC Parameters in a β-Thalassemia Disease Model

- Reduction 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
This is a two part first-in-human, multicenter, randomized placebo controlled single ascending and multiple dose study to assess the preliminary safety, tolerability, PK and efficacy of SLN124 administered subcutaneously for the treatment of non-transfusion dependent thalassemia and low risk myelodysplastic syndrome.

**Study design**

> Part A:

  - Single dose escalation study to evaluate the dose response to SLN124 with a view to identify the most appropriate dose to bring forward into the multiple dose portion of the study
  - Primary aim to determine the safety and tolerability of SLN124 for the treatment of non-transfusion dependent β-thalassemia

> Part B:

  - Bring forward the most efficacious and best tolerated dose to evaluate multiple administrations of SLN124 on hematologic parameters in patients with β-thalassemia and MDS
  - Primary aim to determine the safety and tolerability of multiple doses of SLN124 for the treatment of non-transfusion dependent β-thalassemia and low risk myelodysplastic syndrome
SLN124 Summary

• **Preclinical package:** Robust data generated in several disease models.

• **Status:** Non-clinical development work ongoing, with CTA filing expected in Q2 2019. Orphan Designation granted for β–Thalassaemia and application planned for MDS.

• **Clinical plans:** Phase 1b planned in patients (β–Thalassaemia and MDS). Network of KOL’s established.

• **Dosing regimen:** Patient-friendly, with monthly or less frequent dosing expected and subcutaneous administration route.

• **Regulatory:** Positive feedback received at Scientific Advice meetings with both the UK (MHRA) and German (BfArM) national regulators.

• SLN124 is well positioned for **commercial success** against current standard of care and other medicines in development.
SLN360 for the treatment of Cardiovascular disease with high Lp(a)
SLN360 targets Lp(a) - an **Independent** Risk Factor for CVD

> Lp(a) is a lipoprotein involved in the transportation of lipids.

> **Lp(a) is a validated target in humans.** Lp(a) excess is detected in patients with premature CVD:

  • High Lp(a) is associated with CHD, unstable angina, myocardial infarction (MI) and other CVD complications
  
  • High Lp(a) levels have been shown to predict a 2-4 fold increase in risk of MI and CVD
  
  • Adding Lp(a) levels ≥80th percentile to conventional risk factors improves MI and CHD risk prediction

> Lp(a) is only **minimally confounded** by typical risk factors such as smoking, blood pressure or diabetes.

> **High unmet need - Apheresis is the only approach that can reduce** Lp(a) **levels by a large amount, however is invasive and burdensome:** procedure lasts 70min-2h, can be performed up to every week
Lp(a) has Prothrombotic, Proinflammatory and Proatherogenic Properties

Adapted from Tsimikas et al 2017
Proof of mechanism achieved

Prolonged serum knockdown of Lp(a)

> Multiple dosing at 3mg/kg resulted in sustained reduction of Lp(a) serum levels (>90%) for at least over two months after first dose (max ~>95% KD)

> Similar outcome after single subcutaneous injection of SLN360 at 9mg/kg.

> Over 85% KD at NADIR for single 3mg/kg injection with 50% KD still observed after 2 months post treatment
Rationale

> Lp(a) is a low-density lipoprotein produced predominantly by the liver and composed of Apo(a) and Apo B, both hepatocyte expressed genes.

> Genetically defined high Lp(a) serum levels are unaffected by diet and exercise and are an independent risk factor for CVD. There is no specific Lp(a) targeting therapy available at the moment.

> An LPA silencing siRNA would provide a specific, safe and durable approach for reducing Lp(a) levels in high risk patients.

Our Programme

> A potent lead sequence has been selected and tested in vivo in non-human primates (NHP).

> Proof of mechanism has been achieved in NHP: dose dependent reduction in both LPA (liver mRNA) and Lp(a) (serum protein) observed, with max 95% KD observed after multiple dosing.

> Our drug compares positively against published data by competitors, suggesting a superior performance.

> IND/CTA is planned for H2 2020
Complement-mediated diseases
GalNac siRNAs for the treatment of Complement-mediated diseases

Schematic overview - complement system

Targeting the complement system offers a broad indication spectrum (such as Paroxysmal Nocturnal Hemoglobinuria, Myasthenia gravis, C3 Glomerulopathy, atypical Hemolytic Uremic Syndrome or Cold Agglutinin Disease)

- **The Complement system** is part of the innate immune system and consists of 3 pathways
- > 30 serum proteins (many thereof produced in hepatocytes)
- It represents an activation cascade with various effector functions, such as MAC (membrane attack complex) formation for pathogen destruction and activation of immune cells
- First drug on the market targeting the complement pathway is Eculizumab (Soliris, C5 Ab)
- **There is unmet need** because Eculizumab is not consistently effective for all patients (mutations, non responders) and indications

Mastellos et al., 2015
Complement-mediated diseases
Initial results: Proof of Mechanism in vivo (mouse)

Study design:
- n=4 healthy mice per group, serum sampling at day -3, 4, 10 and 14, liver tissue at day 14
- siRNAs: non-optimized GalNac conjugated chemistry

Target knock down:
> 80 % mRNA & protein knock down achieved using non-optimized siRNAs

→ Identification of 2 potent siRNA sequences for lead optimization and NHP studies (using advanced chemistry)
Summary & Outlook
## Expected Newsflow & Company Milestones

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<th>2020</th>
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<td>First In Human Dosing</td>
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<td>First Interim Results</td>
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<td><strong>SLN360</strong></td>
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<td>Clinical candidate nomination</td>
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<td><strong>2018 New Targets</strong></td>
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<td><strong>Quark Out-License in QPI-1002</strong></td>
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<td>First interpretative results for DGF Phase 3 study expected</td>
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**Notes:**
1. MDS = Myelodysplastic syndrome
2. As of 31st Dec 2018

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HQ in London

R&D in Berlin

Approx. 50 employees across both sites