Silence Therapeutics

Corporate Presentation

July 2020
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# Silence Therapeutics - Summary

<table>
<thead>
<tr>
<th>Valuable Platform</th>
<th>Reproducible, proprietary gene silencing (RNAi) therapeutics platform, rapidly generating internal pipeline and out-licensing options. The potential of our platform has been validated through collaborations with AstraZeneca, Mallinckrodt and Takeda</th>
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<tbody>
<tr>
<td>Growing Clinical Pipeline</td>
<td>SLN360 (CVD with high LP(a))&lt;br&gt;SLN124 (β-Thalassemia and MDS&lt;sup&gt;1&lt;/sup&gt;)&lt;br&gt;SLN500 (C3, complement mediated disease)</td>
</tr>
<tr>
<td>Strong Experienced Team</td>
<td>Pioneers in siRNA for over 18 years, growing clinical team, and experienced biopharma Board and Management team</td>
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<tr>
<td>Target Selection</td>
<td>Focused on targeting indications in rare diseases and large population targets, including new medicines for cardiovascular disease and complement-mediated diseases</td>
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<td>Strong Financial Position</td>
<td>Strong financial position with a cash runway extending beyond key clinical milestones such as SLN360 and SLN124 Phase I trial readouts. £90m pro-forma financial resources at end March 2020.</td>
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</tbody>
</table>

**Notes:**

1. MDS = Myelodysplastic syndrome

**HQ in London**

**R&D in Berlin**

**+ New office in New York**

Approx. 50 employees across all sites
Leadership

Executive Chairman
Iain Ross

➢ Appointed as Chairman in April 2019 and Executive Chairman in Dec 2019 until new CEO is appointed
➢ Over 40 years’ experience in the international life sciences and technology sectors, where he has completed multiple financing transactions, multiple IPOs and has over 25 years in cross-border management as Chairman and CEO

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 Biocarin for $680m
➢ Most recently CMO at Albumedix
➢ Spent 4 years in senior R&D roles at Novartis
➢ Medical degree and doctorate from Bristol University

CFO
Rob Quinn

➢ Chartered accountancy training at Deloitte before joining GSK
➢ Area Finance Director for Africa and Developing Countries at GSK
➢ Joined Silence in early 2017 as Head FP&A
➢ PhD in Biochemistry from the University of Manchester
GalNAc (Ligand) Conjugation Allows for Delivery of siRNA to Liver Cells

Liver-specific and long-lasting siRNA activity after internalization of GalNAc conjugate
Reproducibly Silencing Disease-Associated Genes Using our Proprietary Platform Technology

**Platform delivery technology**: 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\(^1\).

\(^1\) Well tolerated in animal models tested.

~7,000 proteins expressed in the liver. Silence can target any of them by adapting the siRNA sequence, using the same technology.
A Competitive Platform, With Continuous Fine-Tuning to Further Improve Performance

**SLN360**

Modification pattern: number of non-natural modifications reduced from c.50% to <15% through the discovery of novel modification patterns

End stabilization: increased circulation half-life, increased activity and duration of action

Linker: simplified and flexible synthesis, increased activity, and option to control circulation and intracellular half-life

GalNAc: 2-3 fold increase in activity achieved through optimization of number and placement of GalNAc units

IP: 10 siRNA chemistry patent applications filed 2017-2019

**AMG 890**

AMG 890 chart reproduced from Melquist et al "Targeting apolipoprotein(a) with a novel RNAi delivery platform as a prophylactic treatment to reduce risk of cardiovascular events in individuals with elevated lipoprotein(a)" AHA 2016 Scientific Sessions

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## Development Pipeline

<table>
<thead>
<tr>
<th>Programme</th>
<th>Disease</th>
<th>Target</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Proprietary/Partnered</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>SLN360</td>
<td>Cardiovascular disease with high Lp(a)</td>
<td>Lp(a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IND expected to be filed in H2 2020</td>
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<tr>
<td>SLN124</td>
<td>6-Thalassaemia</td>
<td>TMPRSS6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clinical start expected in 2020</td>
</tr>
<tr>
<td>SLN124</td>
<td>Myelodysplastic Syndrome</td>
<td>TMPRSS6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IND/CTA expected in H2 2021</td>
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<tr>
<td>SLN500</td>
<td>Complement-mediated diseases</td>
<td>C3</td>
<td></td>
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Collaboration with AstraZeneca for the Treatment of Cardiovascular, Renal, Metabolic and Respiratory Diseases

• **March 2020: Research, Collaboration, Option and Licence agreement to discover and develop siRNA therapeutics for the treatment of serious diseases.**

  > Draws on Silence’s extensive experience in the development of siRNA therapeutics, together with AstraZeneca’s industry leading expertise in disease biology and target identification, to develop first-in-class and differentiated therapeutics to address significant unmet need.

  > Five targets anticipated to be started within three years with AstraZeneca having the option to extend the collaboration to a further five targets.

  > Silence’s GalNAc-siRNA platform to be harnessed for liver expressed gene targets. Both parties to collaborate to achieve targeted delivery of siRNA molecules to other tissues including heart, kidney and lung.

  > Silence will be responsible for designing siRNA molecules against gene targets selected by AstraZeneca, and for manufacturing of material to support GLP toxicology studies and Phase I clinical studies.

  > Silence will have the option to negotiate for co-development of two programs of their choice starting from Phase II.

> $60 million cash upfront and $20 million equity investment.

> Total deal value over $4 billion

> Option fee of $10 million per target at the point of candidate nomination. Up to $140 million in development milestones and up to $250 million in commercialisation milestones. Total milestones of up to $400 million per target.

> High single digit to low double-digit royalties on net sales for each target.
Our siRNA Platform is Validated Through Strategic Partnerships with Leading Pharma Companies

January 2020 - Silence Therapeutics entered into a Technology Evaluation Agreement with Takeda to explore the potential of Silence’s platform to generate siRNA molecules against a novel, undisclosed target discovered by Takeda.

> Takeda will provide Silence with single-digit millions USD of research funding
> Silence and Takeda have further agreed to negotiate the terms of a License Agreement should the initial evaluation study prove successful

July 2019 - Silence Therapeutics entered into a Research and Collaboration Agreement with Mallinckrodt for the development of RNAi therapeutics targeting the complement system. The agreement included SLN500, Silence’s preclinical asset targeting C3, and options on two further complement targets.

> $20 million cash upfront and $5 million equity investment
> Total deal value $2.1 billion – up to $673 million in milestones for SLN500 and up to $713 million in milestones for each additional target
> Silence will be responsible for development activities until the end of Phase 1, after which Mallinckrodt will assume clinical development and responsibility for global commercialization
> Mallinckrodt will cover the costs of the Phase 1 study and GMP manufacture
> Low double-digit to high-teen royalties on net sales for SLN500 and each optioned asset
SLN360 for the treatment of Cardiovascular Disease with high Lp(a)
Lp(a): What is it?

Discovered in 1963 by Kare Berg
Expressed predominantly in the liver

- Highly variable in size
- Expression restricted to human and non-human primates
Lp(a) levels are genetically defined
- Not modified through lifestyle interventions

Contributes to total LDL-C
Considered to be pro-atherogenic, pro-thrombotic and pro-inflammatory

Major untreated risk factor in CVD
- Currently approved therapies do not address Lp(a)
Most biological entities show a normal distribution in a population. Lp(a) distribution is skewed with 20% of the population with higher than 50 mg/dL.
Cardiovascular event risk increases with high Lp(a)

Risk Ratio:
- The probability of one outcome versus another.
- A risk ratio of 2 is double the risk.
- A risk of 0.5 is half the risk

Top 10% Lp(a) ~90mg/dL

- Ischemic Stroke: 1.2 to 1.6
- Mortality: 1.2 to 1.4
- Myocardial Infarction: 2 to 3
- Heart failure: 1.6 to 1.8
- Aortic Stenosis: 2 to 3
Up to 700 million globally in top 10% Lp(a) levels

### Global Prevalence of Elevated Lp(a) [millions]

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>20%</th>
<th>10%</th>
<th>5%</th>
<th>1%</th>
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<tbody>
<tr>
<td>Lp(a) [mg/dL]</td>
<td>60</td>
<td>90</td>
<td>116</td>
<td>180</td>
</tr>
<tr>
<td>USA</td>
<td>64</td>
<td>30</td>
<td>16</td>
<td>3.2</td>
</tr>
<tr>
<td>EU</td>
<td>150</td>
<td>75</td>
<td>37.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Globally</td>
<td>1400</td>
<td><strong>700</strong></td>
<td>350</td>
<td>70</td>
</tr>
</tbody>
</table>


Source: US laboratory Database in 531,144 patients
SLN360 Targets Lp(a) - an Independent Risk Factor for Cardiovascular Disease

- Lp(a) levels are genetically determined
- Recognized as a major untreated risk factor in cardiovascular disease
- Lp(a) levels are not significantly modifiable through diet or approved pharmacological therapies
- Large population worldwide with up to 10% with >90mg/dL (2x increased MI risk)
- Multiple mechanisms by which Lp(a) causes CVD
  - > Pro-atherogenic
  - > Pro-thrombotic
  - > Pro-inflammatory

Targeting Lp(a) with SLN360 has the potential to address major unmet needs in cardiovascular disease
Sustained and Deep LP(a) Knockdown Demonstrated in Animal Model

Prolonged serum knockdown of LP(a) in NHP
- 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 Program

> 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 is planned for H2 2020
SLN124 for the treatment of Iron Overload Disorders
Market Opportunity of SLN124

US and EU patients

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Number</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Thalassemia</td>
<td>~40,000 TDT&lt;sup&gt;1&lt;/sup&gt;</td>
<td>From birth, but notable incidence of NTDT beyond 35</td>
</tr>
<tr>
<td>~20,000 NTDT&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS&lt;sup&gt;3&lt;/sup&gt;</td>
<td>&gt;100,000</td>
<td>Typically &gt;70y</td>
</tr>
</tbody>
</table>

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

Standard of Care

Advantages vs Competition

- Quality of Life
- Safety
- Organ iron levels
- Compliance
- Less frequent dosing
- SoC: Transfusions + Chelators
- Antisense RNA
- Luspatercept
- Gene therapy
- Hepcidin mimetics

Limitations:
- Toxicity
- Lack of compliance
- Slow iron reduction
- Intolerance
- Insufficient

Notes:

- ~40,000 TDT
- ~20,000 NTDT
- >100,000 MDS
- >100,000 β-Thalassemia
- Onset: from birth, but notable incidence of NTDT beyond 35
- Onset: Typically >70y
- Orphan indications
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
SLN124 Ameliorates Splenomegaly and Improves Anemia in β-Thalassemic Mice

**Study design**
- Hbb<sup>α3+</sup> mice, 2–4 m, n=5–8
- 2x 3mg/kg SLN124 s.c.
- 1.25 mg/ml deferiprone in drinking water

**Collaboration with**
- Dr. J. Vadolas & Dr. G. Grigoriadis
- Monash Medical Centre/Melbourne, Australia

### Hemoglobin
- Hb ↑ by ≥1.5 g/dL defined as "clinically relevant effect"<sup>1</sup>
- No ∆ Hb with 5-weeks DFP exposure
- ↓ need for blood transfusions by ↑ Hb (reflects 2-3 units of RBC)<sup>2</sup>

### Spleen weight
- SLN124 ameliorates splenomegaly; no impact by iron chelator DFP
- SLN124 improves anemia and ↓ the need for RBC transfusions
- No effect by DFP alone, SLN124 effect maintained in the presence of DFP

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<sup>1</sup> Platzbecker et al., Blood 2019; <sup>2</sup>Bosch et al., Vox Sang 2017
SLN500 for the treatment of Complement-Mediated Diseases
Complement as a Target Cascade

C3 - Hub of the complement cascade

> Complement belongs to the innate immune system
> Over 30 serum proteins
> Three pathways converge to form C3 convertases
> Function: MAC formation and immune cell activation
> Eculizumab (anti-C5 Ab): First FDA-approved drug for complement mediated diseases

SLN500 is a promising therapeutic approach allowing for blockade of complement activation downstream of C3

MAC: Membrane attack complex
Attractive Market Size
Combined Opportunity in Multiple Orphan Indications

- IgA Nephropathy
  - Potential indications for C3 siRNA
  - C3 Glomerulopathy
  - Paroxysmal Nocturnal Hemoglobinuria

- aHUS
  - Atypical Haemolytic Uremic Syndrome
  - ~1.5-4.5K patients

- PNH
  - ~10-15K patients
  - Est. combined prevalence

- LN
  - Lupus Nephritis
  - ~240K patients

- AIHA
  - Autoimmune Haemolytic Anemia (Cold Agglutinin Disease & Warm Antibody AIHA)
  - ~140K patients

- IgAN
  - ~350K patients

- MG
  - Myasthenia Gravis
  - ~80-150K patients

- ANCA-AV
  - Antineutrophil Cytoplasmic Autoantibodies - Associated Vasculitis
  - ~30-150K patients

- Other indications:
  - aHUS
  - ~80-150K patients
  - ANCA
  - ~30-150K patients
  - AIHA
  - (~140K patients)
  - MG
  - (~80-150K patients)

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Dose response study with SLN500 in healthy mice

Single ascending doses of SLN500 (0.3 - 5 mg/kg) in healthy mice produce a reduction in both C3 mRNA and protein levels in a dose response manner.
Rationale

 Activation of the complement system is a pathologic feature of several diseases (such as C3 glomerulopathy, paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome and myasthenia gravis).

 Mutations and/or deficiencies in complement regulating factors or stabilizing autoantibodies of convertases are evident in patients with complement-mediated diseases.

 C3 represents a hub in the complement cascade where all three pathways converge.

 Blocking the complement cascade and its detrimental downstream effects is a promising therapeutic strategy.

 SLN500

 siRNA has significant advantages over other modalities, enabling potent and durable knock-down with a high therapeutic index, allowing for an improved dosing regimen for patients suffering from debilitating diseases.

 Proof of mechanism has been achieved in mice: Dose-dependent reduction in both C3 mRNA and C3 serum protein was observed.

 Collaborative deal signed with Mallinckrodt for C3 and up to 2 other complement targets.

 IND/CTA filing is planned for 2021.
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