Silence Therapeutics Plc
June 2018 Interim Results
Dr David Horn Solomon, CEO
David Ellam, CFO

A new era in RNAi therapeutics

Silence: Operational Highlights

- **New leadership** in place with the recruitment of Dr David Horn Solomon as Chief Executive Officer, an experienced public company biotech CEO, board member and biotech investor.
- **The field is advancing**: Gene-silencing as a therapeutic modality was granted its first drug approval by the FDA on 10 August for *patisiran*, validating RNAi as a class of drugs that now have a clear path to market.
- **Positive regulatory feedback** and **promising data** in clinically validated animal disease models representative of iron overload disorders, increases confidence in Silence's lead candidate **SLN124**, with first patient entered in the Phase Ib study anticipated in H2 2019.
- Out-licenced programme, **QPI-1002** for Prevention of Acute Kidney Injury progressed to Phase III clinical trial by partner Quark Pharmaceuticals, Inc.
- **Patisiran** remains accused of infringement of Silence's Intellectual Property in the United Kingdom and Portugal.

Driving the Business Forward

- Primary emphasis is on advancing our proprietary pipeline of valuable **RNAi-derived** assets to build significant shareholder value and to create innovative products for patients and their caregivers.
- Building expertise around Hematology and Iron Metabolism Disorders.
- Partnering, with additional resources now secured, to validate and advance our pipeline assets.
- Broadening pipeline suitable for Partnering, including Cardiovascular Disease.
- Speed to development – can go from Idea to “First in Human” in 24 months.
- Silence’s Gen 3 GalNAc platform provides fewer non-natural chemical modifications with comparable performance. Gen 4 is about combining design elements that increase potency and duration of action of GalNAc conjugates.
- Management is focussed on increasing US presence, including contact with specialist investors.

Evolution of our GalNAc-siRNA platform

GEN1

2016

- Served to transition to conjugate technology, establishing baseline performance. No FTO

GEN2

2017

- Patents filed
- Clinical stage in 2019 (SLN124) and used in late pre-clinical stage programmes (SLN226, CVD)
- Robust performance, competitive to peers

GEN3

Reduced non-natural modifications

- Patents filed
- Entered pipeline in Q2 2018
- Advantages: Improved safety profile and COGS, and FTO further strengthened

GEN4

2018

Different GalNAc unit numbers and positioning

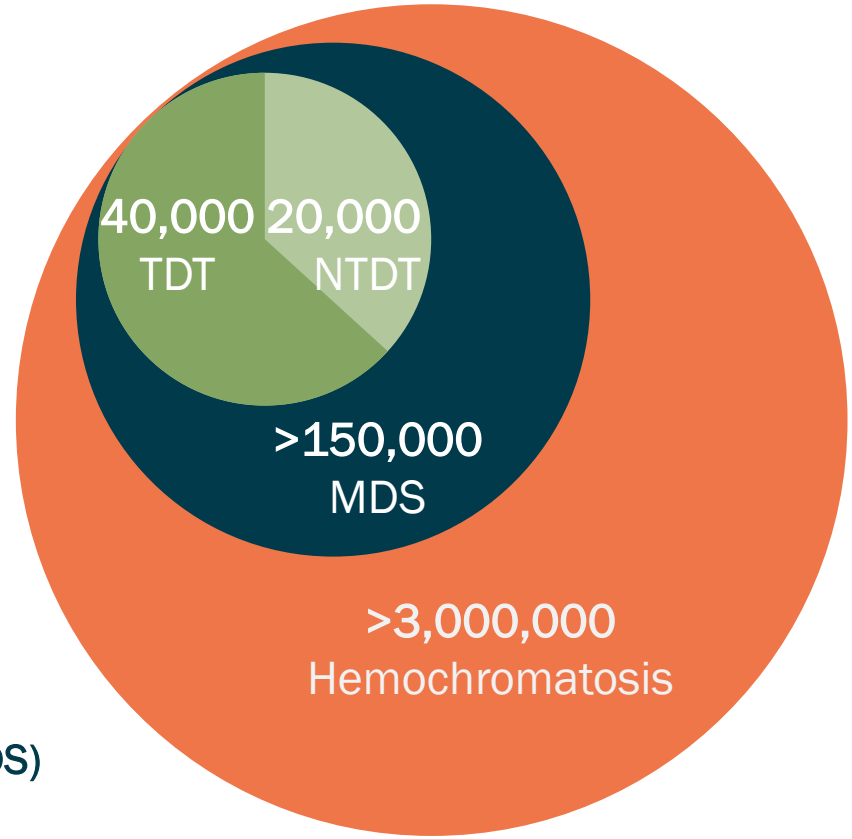
- Patents filed
- Further optimisation ongoing
- Plans to enter the pipeline in early 2019
- Advantages: improved potency, COG and safety

Market opportunity for SLN124 (US and Europe only)

- 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

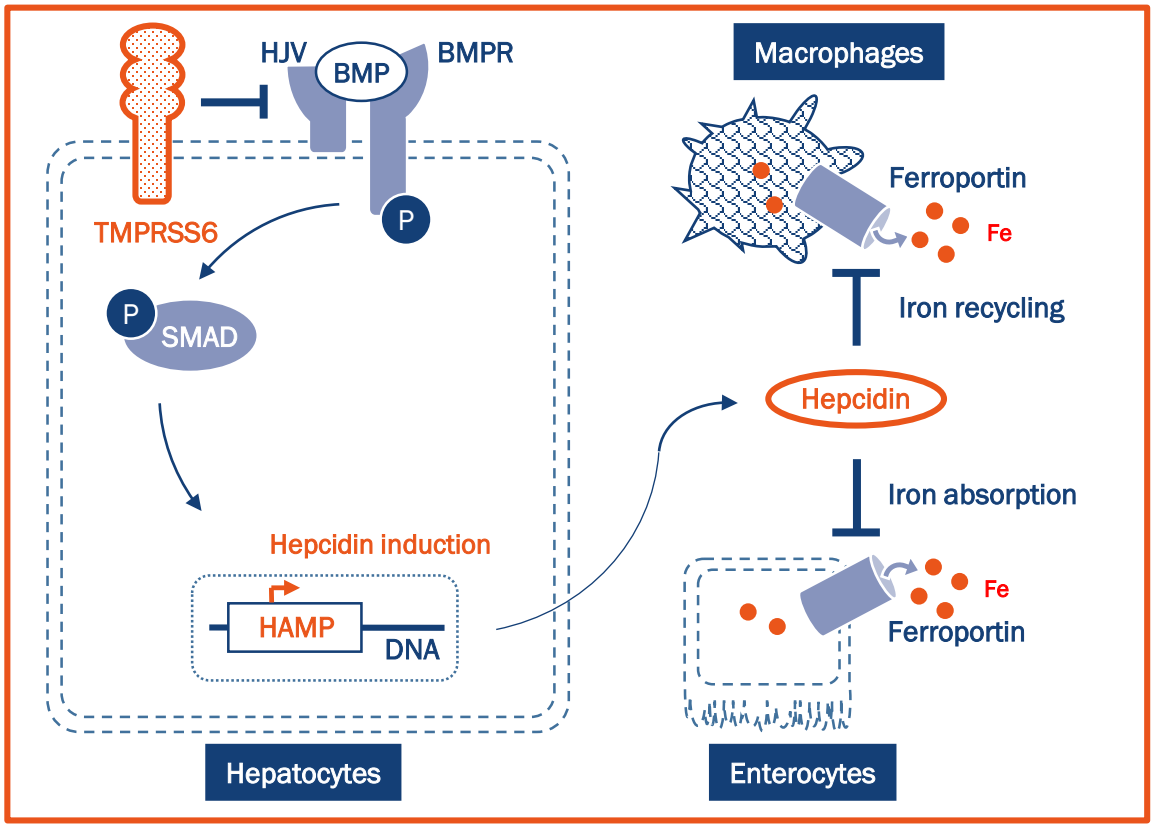
- Myelodysplastic Syndrome (MDS)
- Hemochromatosis



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

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

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

Therapeutic activity of SLN124 in a disease model of Hereditary Hemochromatosis type 1 (iron overload)

Study design

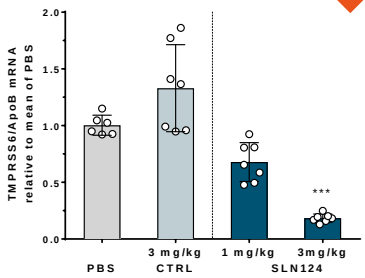
d1 — wk 3

1X sc, HFE$^{-/-}$ mice, females, 6 wks, n=6-7

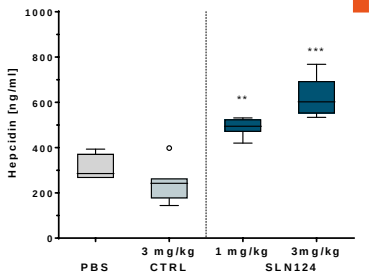
Hfe$^{-/-}$ mice

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

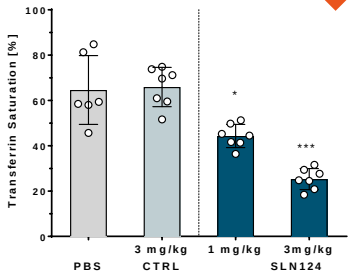
TMPRSS6 mRNA



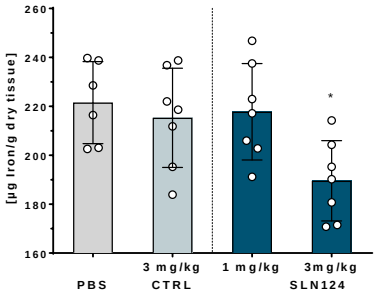
Hepcidin (Serum)



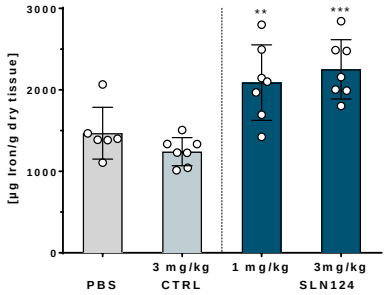
Transf Sat [%]



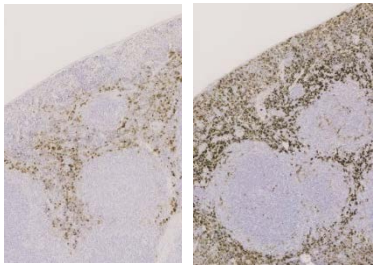
Kidney Iron



Spleen Iron

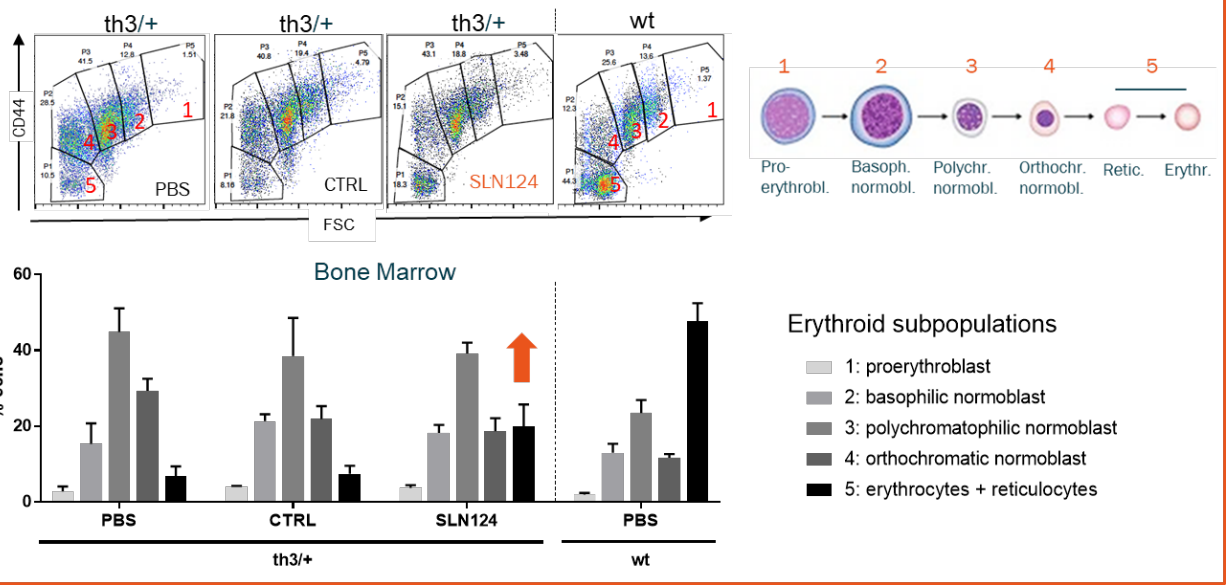


Spleen Iron



- Dose-dependent and **robust silencing of TMPRSS6** mRNA in the liver
- **Induction of hepcidin** expression and **normalisation of iron levels** and transferrin saturation
- **Reduction of tissue iron** levels and redistribution to spleen (physiological storage compartment)

SLN124 improves RBC maturation, anaemia and normalises spleen size in a murine model of β–Thalassaemia intermedia

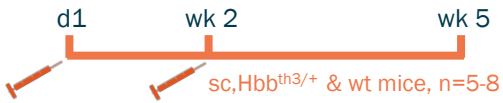


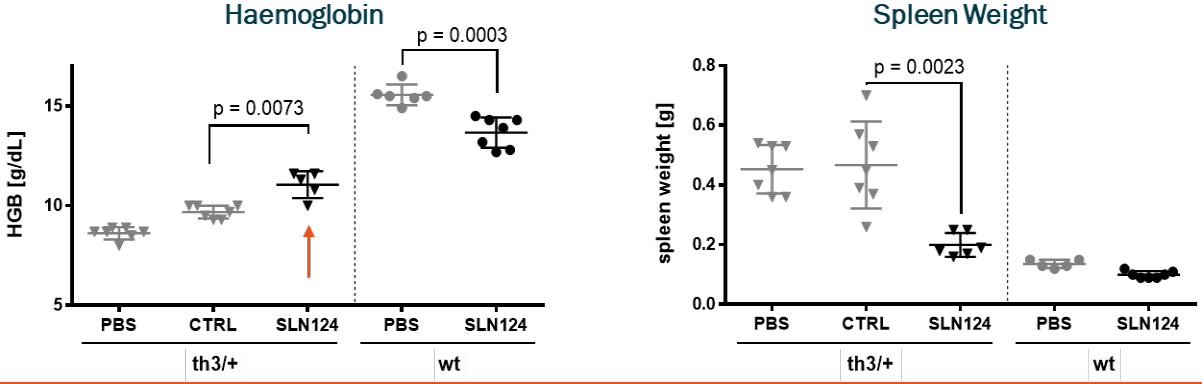
Collaboration with Dr. J. Vadolas & Dr. G. Grigoriadis. Monash Medical Centre/Melbourne, Australia

HUDSON INSTITUTE OF MEDICAL RESEARCH

$Hbb^{th3/+}$ mice

Study design





SLN124 treatment shows promising disease-modifying effects in a clinically relevant model of b-Thalassaemia

SLN124 Summary

- **Preclinical package:** Robust data generated in several disease models
- **Status:** Non-clinical development work ongoing, with CTA filing expected in Q2 2019
- **Clinical plans:** Phase 1b planned in patients (β–Thalassaemia and MDS). Network of KOL's established
- **Dosing regime:** Patient-friendly, with a monthly or less frequent schedule envisaged and subcutaneous administration route
- **Regulatory**: after submitting the SLN124 Briefing Document to the UK Medicines and Healthcare products Regulatory Agency, positive feedback was received at the June Scientific Advice Meeting
- SLN124 is **commercially viable** compared to gene therapy, which has a heavy burden on patients versus a monthly SubQ.

SLN124 is well positioned to offer a potentially safe and potent disease-modifying treatment option to patients living with iron overload disorders, such as β–Thalassaemia (both TDT and NTDT patients)

Silence Therapeutics Plc

David Ellam, CFO

H1 Financial Report 2018

Increase in Operating Expenses to drive platform and indications

Income statement (GBP '000)	2018 H1	2017 H1	2017 Full year
Revenue	0	16	16
Research and development costs [1]	(5,212)	(3,817)	(7,943)
General & Administration expenses[2]	(4,681)	(3,021)	(6,464)
Operating loss	**(9,893)**	**(6,822)**	**(14,391)**
Other income[3]	106	166	10,616
Tax	1,100	1,140	2,157
Net result for the period (after tax)	**(8,687)**	**(5,516)**	**(1,618)**

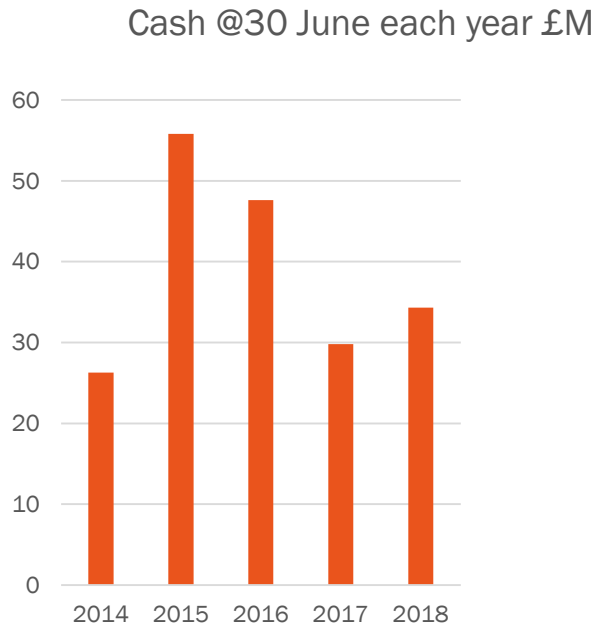
[1] £1.4M increase is higher CMC costs & outsourcing of clinical operations costs, offset by reduced headcount

[2] £1.7M increase is mainly Litigation costs (£1.3M increase from £0.2M prior period) as well as £0.2M increase in payroll costs due to investment in key hires

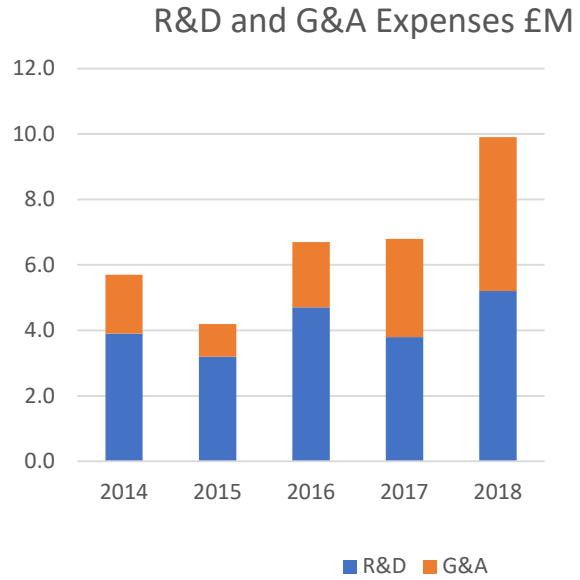
[3] Full year 2017 included £9.1M gain on sale of Arrowhead shares and £1.3M gain on reclassification of FX gains on reclassification of foreign subsidiary.

Silence has >12 months cash to continue to advance the business

Cash, cash equivalents & term deposits of £34.3M at 30 June 2018 ($45.1M)



R&D and G&A Expenses @ 30 June each year



In the last 12 months, Silence received £18.4M proceeds from sale of ARWR shares, having spent £9.2M to acquire those shares in the prior 12 months

Excluding Litigation & Patent costs, R&D runs at
60% of total costs for last two periods

Expected newsflow outlook & milestones next 15 months

	Q4 2018	H1 2019	H2 2019
SLN124			
CTA enabling toxicology	⊙		
File CTA		⊙	
First In Human dosing			⊙
CV disease			
pPoC in NHP	⊙		
2018 new Targets			
POM data available	⊙		
pPOC in mice		⊙	⊙
Final candidate nomination			⊙
Alcohol Use Disorder			
CTA enabling toxicology			⊙
Platform Strengthening			
Gen3 design in use for new targets	⊙		
Gen4 toolbox validated and in use		⊙	
Quark Out-License in QP-1002			
First interpretative results for DGF Phase III study expected	⊙		
Alnylam Litigation			
UK court hearing	⊙		
Expected UK court hearing verdict		⊙	