EDISON

Silence Therapeutics

Initiation of coverage

Solving disease by targeting genes with siRNA

Pharma & biotech

We are initiating coverage of Silence Therapeutics (SLN), a developer of siRNA drugs for diseases that can be genetically targeted. Silence has a proprietary platform for developing siRNA therapeutics, the strength of which was highlighted by preclinical development deals with Mallinckrodt and Takeda (details below). The company will also be re-entering the clinic in Q120 with SLN124, its own drug for iron overload. We are initiating with a valuation of £345m or 440p per share.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
12/17	0.0	(13.5)	(7.7)	0.0	N/A	N/A
12/18	0.0	(19.8)	(25.2)	0.0	N/A	N/A
12/19e	2.1	(18.2)	(20.8)	0.0	N/A	N/A
12/20e	5.8	(22.1)	(24.2)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Takeda and Mallinckrodt deals endorse platform

Silence announced in July 2019 that it signed a deal with Mallinckrodt for the rights to an undisclosed C3 complement inhibitor, SLN500. The deal included $20m upfront, up to $673m in milestone payments (of which $2m has been delivered), double-digit royalties and options on two other complement assets. The company also announced in January 2020 that it entered an agreement with Takeda to investigate a novel undisclosed target, which Takeda will support with single-digit million dollars in research funding (licensing to be discussed later). We see both of these deals as a validation of the strength of the company's technology and IP.

SLN124: Targeting iron overload anaemias in Q120

Iron overload is a disorder that is seen typically in patients who require many repeated transfusions such as those with the genetic disease beta-thalassemia or myelodysplastic syndrome (among others). These diseases affect approximately 10 and four patients per 100,000 in Europe, respectively. The company will begin testing SLN124 in patients in a Phase Ib clinical study in Q120. The drug increases levels of hepcidin, a key regulator of iron uptake, which inhibits the absorption of dietary iron and its release from internal stores.

Aiming for the big fish of cardiovascular disease

Silence also has the preclinical asset SLN360, which knocks down Lp(a), a low-density lipoprotein that is strongly and independently associated with negative cardiovascular outcomes. Silence intends to file an IND in 2020 and we expect it to seek a partner to help finance the expensive cardiovascular outcomes studies.

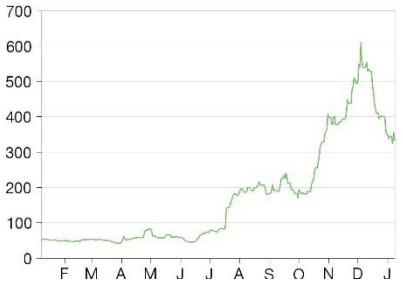
Valuation: Initiated at £345m or 440p per share

Our initial valuation of £345m or 440p per share is based on a risk-adjusted NPV analysis of the firm's assets and revenue streams and is driven primarily by our valuation of SLN124 (£141m). We forecast that it will require £105m in additional capital to reach profitability in 2026, offset by potential business development deals.

9 January 2020

Price	**334p**
Market cap	**£262m**
	US$1.25/£
Net cash (£m) at 31 December 2019	33.5
Shares in issue	78.4m
Free float	45.4%
Code	SLN
Primary exchange	AIM
Secondary exchange	OTCMKTS

Share price performance



%	1m	3m	12m
Abs	(38.2)	85.6	527.8
Rel (local)	(40.8)	73.0	461.4
52-week high/low		610p	41p

Business description

Silence Therapeutics (SLN) has a portfolio of siRNA drugs in early stage testing. SLN124 for iron overload is the most advanced and is entering the clinic in Q120. SLN360 is being developed for cardiovascular disease and is targeting an IND filed in H220. Silence recently signed a deal with Mallinckrodt for rights to the preclinical complement inhibitor, SLN500, and a deal with Takeda to pursue an undisclosed target.

Next events

Initiate SLN124 Phase Ib	Q120
SLN124 interim results	H220
SLN360 IND	H220

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Edison profile page

Investment summary

Company description: siRNA for significant medical problems

Silence has developed a platform technology for producing short interfering ribonucleic acid (siRNA) therapeutics to treat a range of disorders. The company's technology focuses on using double-stranded, blunt-ended oligonucleotides targeted to hepatocytes using GalNAc (N-acetylgalactosamine). The robustness of this technology was recently vetted by two preclinical development deals signed by the company: with Mallinckrodt for assets to treat complement system disorders ($20m upfront and $673m in additional milestones and double-digit royalties) and with Takeda for an undisclosed target and indication (single-digit million dollars in research funding, future licensing discussions). The company will enter the clinic in Q120 with its own asset, SLN124, for the treatment of iron overload (see page 5) as a consequence of beta-thalassemia or myelodysplastic syndrome (MDS); it also has plans to file an IND in H220 for its cardiovascular (CV) drug, SLN360 (see page 10). Finally, the company has single-digit royalty streams on the Phase III drug QPI-1002 being developed by Quark and Onpattro (patisiran) developed by Alnylam.

Valuation: Initiated at £345m or 440p per share

We arrive at an initial valuation of £345m or 440p per share based on a risk-adjusted NPV analysis. This valuation is driven predominantly by SLN124 (£141m), with a large portion of the remainder attributable to SLN360. Additionally, we include provisional royalty streams for SLN500 and the Takeda programme (using $400m peak sales as a placeholder for both) as the indications have not been announced for the programmes; we expect to amend this when more information is released (although we do include $408m in risk-adjusted milestones for each).

Financials: £105m to reach profitability in 2026

Silence is a loss-making company reporting £18.3m in losses in 2018, and we expect similar expenses in 2019, offset by the payments from Mallinckrodt (£15.1m 2019 net loss is projected, £16.1m deferred revenue). We expect these losses to increase as the company enters the clinic with SLN124 and advances its other programmes; we forecast £20.0m in 2020 R&D expenses. We expect the company to require an additional £105m in financing to reach profitability in 2026, which we include as illustrative debt (£30m in 2021, £30m in 2022 and £45m in 2024). This does not include an SLN360 pivotal study, which we expect the company will need to secure a partner to support and which might offset other financing needs.

Sensitivities: Early stage but robust platform

The challenges faced by Silence are not unlike those faced by other small, early stage biotechnology companies. The greatest risks faced by the company at this time are clinical in nature, although they are at least somewhat mitigated by Silence's particular circumstances. The constructs being examined are known to be specific for their target genes in model systems, and given the particulars of RNA-based drug development, the pharmacokinetics and targeting of the constructs can be expected to be very similar to other drugs of this class also targeting the liver. However, it can be difficult to predict the potency of RNAi therapeutics in humans before testing and none of the company's drugs in development have been tested in humans yet. In addition to clinical risk, the company faces significant financial and commercial hurdles. All of the indications that Silence has announced that it is investigating are competitive, with multiple existing therapies and programmes in development. Finally, the company faces financing risk as it will need to raise an estimated £105m to reach profitability in 2026, although this may be offset through partnering deals.

Silence Therapeutics: Ready to re-enter the clinic

Silence Therapeutics is a longstanding player in the development of RNA-based therapeutics. The company has developed a series of RNA interference (RNAi) drugs that employ a short interfering RNA (siRNA) motif and holds some of the foundational IP in the space. The company spent significant time and effort defending this IP, but in 2018 the company settled its longstanding lawsuit with Alnylam, hired new management and began preparations to bring this technology to the clinic. The company is currently in the process of hiring a new CEO after the departure of the previous CEO in December 2019. Chairman Iain Ross, who founded the business through the merger of SR Pharma and Atugen back in 2006, is now overseeing the company. He left the business in 2010 but returned as chairman in April 2019, and is in the process of hiring a new CEO to lead the management team that has been put in place over the last 18 months.

The value of company's technology has recently been highlighted by two major deals. The company announced in July 2019 that it has entered into a licensing agreement with Mallinckrodt to develop SLN500, a C3 complement inhibitor for an undisclosed complement-mediated disease or diseases (more on the agreement below). The company has announced that it plans to file an IND for the programme in 2021. Mallinckrodt additionally acquired options on two other undisclosed complement-targeted siRNA drugs in the agreement. Additionally, the company recently entered into a collaboration agreement with Takeda to develop a drug against a novel, undisclosed target. Neither company has disclosed the indication that will be studied or the details of the agreement outside that Takeda will provide single-digit million dollars in research support.

Silence is also internally developing a suite of siRNA drugs targeting diseases of the blood and circulatory system. Its lead product is SLN124 for the treatment of iron overload secondary to beta-thalassemia (see page 8) and myelodysplastic syndrome (see page 9). It expects to enter the clinic in Q120 and the drug has an orphan drug designation from the EMA. The company is also developing SLN360 for the prevention of cardiovascular disease. This product is in preclinical testing with an IND filing planned for H220.

Silence also previously out-licensed its siRNA stabilisation chemistry (marketed as the AtuRNAi technology) to Quark Pharmaceuticals. Quark is developing QPI-1002 using AtuRNAi for the treatment of delayed graft function (DGF) and acute kidney injury (AKI), both of which are in Phase III studies and partnered with Novartis. Finally, the company is due small royalties on EU sales of Onpattro (patisiran; approved for hereditary transthyretin hATTR amyloidosis) stemming from its settlement.

Exhibit 1: Silence Therapeutics programmes

Asset	Indication	Stage	Notes
Proprietary programmes			
SLN124	Beta thalassemia	Preclinical	Targeting first patients in Q120
	Myelodysplastic syndrome	Preclinical	First patients to be included in Phase Ib in ~2021
	Undisclosed	Discovery	
SLN360	Cardiovascular disease	Preclinical	IND/CTA planned for H220
Royalties and licences			
SLN500	C3 complement-mediated disease	Preclinical	Development collaboration with Mallinckrodt
Undisclosed	Complement-mediated disease	Discovery	
Undisclosed	Complement-mediated disease	Discovery	
Takeda programme	Undisclosed	Discovery	Development collaboration with Takeda
QPI-1002	Delayed graft function	Phase III	Platform licensed by Quark
	Acute kidney injury	Phase III	Platform licensed by Quark
Onpattro (patisiran)	Hereditary transthyretin (hATTR) amyloidosis	Approved	Owned and marketed by Alnylam

Source: Silence Therapeutics

Nucleotide technology

Silence's technology and know-how in the nucleotide space is central to its investment case. It is one of the original pioneers in nucleotide based drug design and this legacy has been recognised by other drug developers such as Mallinckrodt and Takeda interested in entering the space. Given how fundamental the company's IP is, the applications of its technology are exceptionally wide, as its nucleotide platform is readily adaptable to a wide range of disorders.

RNAi is the natural process by which gene expression is modulated by oligonucleotides present in cells. A short nucleotide that is complementary to the targeted messenger RNA (mRNA) gene transcript binds to and modifies how the gene is translated into protein, either by inhibiting its translation (ie knocking down) or modifying how the gene transcript is spliced (eg affecting exon skipping). This is a physiologic process by which cells regulate their contents, but the mechanism can be co-opted by therapeutics to modulate these cell contents and thereby affect patient physiology. Developing nucleotide-based drugs involves making chemical modifications to the strand to improve its stability and targeting. The drug itself can be composed of RNA, DNA or a range of other unnatural nucleotides.

There are currently eight approved drugs based on this principle (Exhibit 2), all of which are marketed for the treatment of rare diseases. Note that this does not include Vitravene (fomivirsen, Novartis), the first approved antisense drug, which Novartis ceased marketing in 2006, or Macugen (pegaptanib, Bausch), a non-interfering nucleotide drug.

Exhibit 2: Nucleotide silencing drugs

Product	Drug	Company	Approval	Price	Indication	Technology
Kynamro	mipomersen	Kastle	2013	$179,000	Homozygous familial hypercholesterolemia (HoFH)	Antisense
Exondys 51	eteplirsen	Sarepta	2016	$300,000	Duchenne muscular dystrophy	Antisense
Spinraza	nusinersen	Biogen	2016	$375,000	Spinal-muscular atrophy	Antisense
Onpattro	patisiran	Alnylam	2018	$450,000	hATTR amyloidosis	siRNA
Tegsedi	inotersen	Akcea	2018	$450,000	hATTR amyloidosis	Antisense
Waylivra	volanesorsen	Akcea	2019		Familial chylomicronemia syndrome	Antisense
Givlaari	givosiran	Alnylam	2019	$575,000	Acute hepatic porphyrias (AHPs)	siRNA
Vyondys 53	golodirsen	Sarepta	2019	$300,000	Duchenne muscular dystrophy	Antisense

Source: Evaluate Pharma, Institute for Clinical and Economic Review (ICER)

There are two leading technologies based on these principles. Antisense is the more basic technology and accounts for almost all of the approved treatments to date. An antisense therapeutic, as the term is commonly used in biotech, consists of a single nucleotide strand, which helps improve the cell permeability of the construct. These drugs modify mRNA expression by either blocking their translation by binding tightly to the transcript (steric hindrance) or by triggering RNase H mediated degradation (if the drug contains DNA nucleotides). However, the single-stranded nature of these drugs makes them more unstable, thereby they require extensive chemical modifications to improve their chemical properties.

The competing technology is siRNA, which uses two complementary nucleotide strands and more closely resembles the endogenous RNAi mechanism. This allows the drugs to recruit the enzyme Argonaute (AGO), which aids in the suppression and degradation of the targeted gene transcript. Moreover, the double-stranded nature of these constructs improves their stability both intra- and extra-cellularly. This comes at the cost of reduced cell permeability and these drugs require targeting mechanisms to deliver them to cells. One method of improving permeability is to complex the siRNA with a lipid nanoparticle, which should enable its delivery to a range of different tissues. The first approved siRNA drug, Onpattro, is composed of a construct encapsulated in a lipid nanoparticle.

However, in cases where the therapy is targeted at the liver, conjugation to GalNAc has emerged as the dominant strategy. GalNAc is a ligand of the asialoglycoprotein receptor (ASGPR) and when

bound, triggers the endocytosis of the construct. Oligonucleotides naturally concentrate in the liver, so this strategy leverages this fact to efficiently deliver therapy to these cells. This is the strategy currently employed by Silence.

An additional key aspect of Silence's technology is the use of 'blunt-ended' nucleotide strands. Oligonucleotides can either have overhangs, where short stretches (typically two bases) at the ends of the construct are single stranded, or be blunt-ended, where there are no single strand overhangs. There is evidence to suggest that blunt-ended siRNA can reduce the risk of off-target effects, where unrelated genes are modulated.[1]

Silence has an extensive, if ageing, patent estate with over 50 patents granted to date. The foundational patents covering the technology were largely filed around 2002, including the patent allegedly infringed by Alnylam. This foundational IP is important because even though it expires soon, it is what provides Silence one of the limited licences to operate in the RNAi space at this time. Moreover, the company continues to expand its patent estate and has filed 10 patent application families since 2016 on the underlying technology. The company also patents the individual sequences used in its therapies, although we expect the most robust IP protection to be from biologic exclusivity (12 years in the US and 10 in Europe).

SLN124

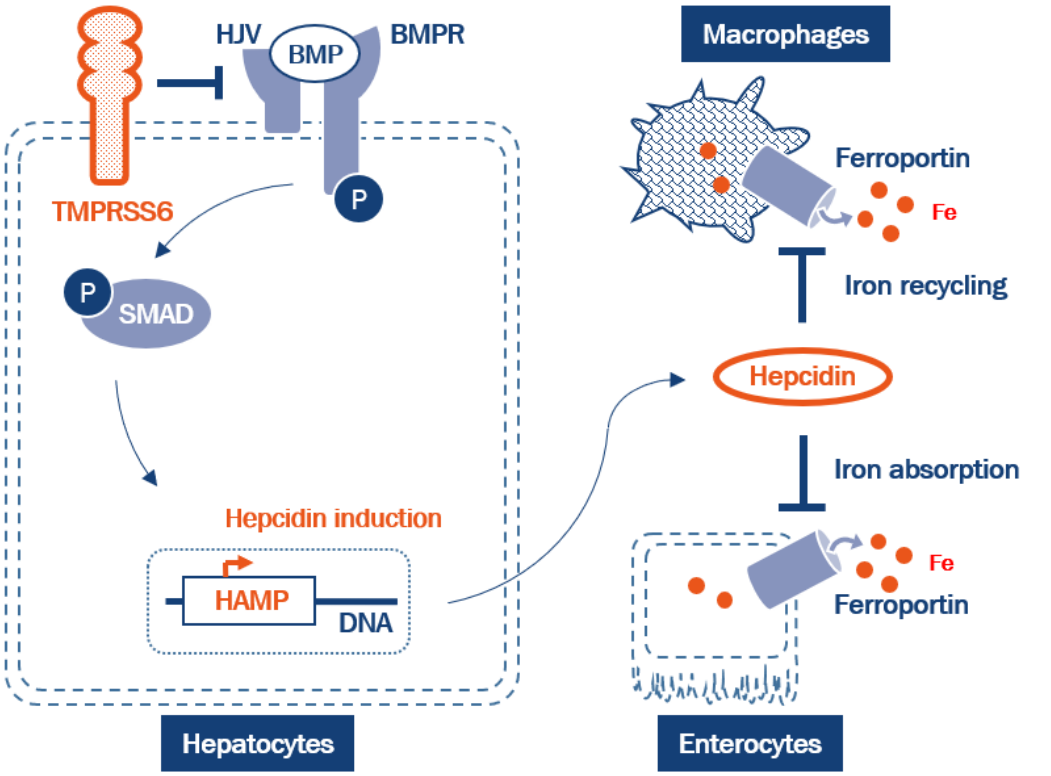
SLN124 is Silence's most advanced development programme and is expected to enter clinical trials for the treatment of iron overload (secondary to beta-thalassemia and MDS) in Q120. The drug knocks-down the expression of the protein TMPRSS6, a signalling protein involved in a feedback mechanism that controls serum iron concentrations. The primary site of TMPRSS6 expression is in the liver, which is consistent with the drug's targeting strategy (of using GalNAc). Iron overload is a syndrome caused by the chronic elevation of systemic iron in the body that leads to the uncontrolled accumulation of iron in various organs. Although serum iron concentrations are tightly controlled, unlike many other metabolic systems, there is no dedicated machinery to control the elimination or excretion of iron from the body, and instead it is lost in a slow, steady process primarily from the sloughing of skin cells and the lining of the gut. Therefore, serum iron levels are generally controlled by regulating the absorption of iron from the gut and by sequestering iron in various tissues, but chronic overexposure to iron can lead to the formation of toxic iron deposits. This can cause multiple organ dysfunctions such as liver disease, heart failure and insulin resistance.

TMPRSS6 protein levels are elevated and hepcidin levels are reduced by erythropoietic stimuli (the growth of new red blood cells), either through physiological means or via exogenous erythropoietin hormone.[2] TMPRSS6 is a negative regulator of the expression of hepcidin, the key regulator of the concentration of iron in the blood, controlling both the rate that iron is absorbed by the gut as well as the rate at which it is removed from the blood by the liver and macrophages (Exhibit 3). High hepcidin levels reduce serum iron levels. Therefore, knockdown of TMPRSS6 with SLN124 increases hepcidin, which subsequently reduces circulating iron, thereby potentially protecting against iron mediated toxicities.

[1] Alagia A and Eritja R (2016) siRNA and RNAi optimization. *Wiley Interdisc Rev: RNA* 7, 316–329.

[2] Frýdlová J, et al. (2016) Effect of Erythropoietin, Iron Deficiency and Iron Overload on Liver Matriptase-2 (TMPRSS6) Protein Content in Mice and Rats. *PLOS One* 11, e0148540.

Exhibit 3: Regulation of serum iron via hepcidin and TMPRSS6



Source: Silence Therapeutics

The company is currently targeting anaemia and iron overload as a consequence of beta-thalassemia and MDS, and has an undisclosed earlier-stage indication. Iron overload can be caused by congenital disorders such as hereditary hemochromatosis (HH) or as the side effect of ineffective erythropoiesis and repeated blood transfusions. The latter is the class of iron overload that Silence is currently targeting, as repeated transfusions are common for the treatment of the anaemia caused by both beta-thalassemia and MDS. Blood transfusions introduce patients to large quantities of additional iron (bound in the haemoglobin of red blood cells) that can accumulate after long periods of treatment.

Competitive environment

The standard treatment for iron overload is chelation therapy, although this is associated with potentially life-threatening complications. Chelation is when chemicals that bind iron are introduced to the blood to encourage its elimination. The leading chelation product is deferasirox (available in two formulations as the brands Exjade and Jadenu, both from Novartis), which comes with black box warnings for potentially fatal renal toxicity, hepatic toxicity and gastrointestinal haemorrhage. Exjade retails for $140 per 500mg pill in the US, which translates to approximately $150,000 per patient-year (assuming 20mg/kg daily for 75kg), although we expect the price of this product to reduce with the entrance of generics in the market in 2019. The products had combined sales of $1.1bn in 2018.

There are a small number of other non-chelation products in development for the treatment of iron overload. The most direct competitor with SLN124 is IONIS-TMPRSS6-LRx being developed at Ionis (IONS). It is a TMPRSS6 antisense oligonucleotide and thus has a similar mechanism of action. The drug has been tested in a Phase I study in healthy volunteers and was able to lower serum iron by up to 49% (at the highest dose). Another early stage programme is Vifor Pharma's VIT-2763, which has completed Phase I. VIT-2763 is a small molecule inhibitor of ferroportin, the

transmembrane iron channel that is responsible for iron absorption from the gut. The product was also able to lower serum iron significantly in healthy individuals, but the rate of treatment-emergent adverse events was high (55% to 85%, depending on cohort), although there are limited details.[3]

La Jolla Pharmaceuticals is developing LJPC-401, which is a formulation of recombinant human hepcidin for injection, thereby leveraging the same signalling pathway that SLN124 hopes to target. La Jolla recently stated in November 2019 it is revaluating the development of the drug after it failed to reach its primary endpoint in a Phase II study for beta-thalassemia, but met its endpoints for HH. One potential limitation of the drug is that it appears to be eliminated quickly. High doses showed half-lives of three to four hours in the Phase I study, and although longer retention was seen in lower doses, this may be an effect of endogenous hepcidin production.

Protagonist Therapeutics is developing the similar PTG-300, which is a peptide structurally similar to hepcidin and entered Phase II in Q119. PTG-300 has a longer half-life (over 24 hours), but unlike LJPC-401, it is not identical to endogenous hepcidin and therefore carries more safety and efficacy worries. PTG-300 showed high rates of injection site reaction (42%), headache (20%) and respiratory tract infection (18%) in Phase I. We also note that in both LJPC-401 and PTG-300 serum iron went above baseline after the drug effects wore off.

In addition to the above, we expect the competitive environment for iron overload disorder to be multi-tiered and the product to receive indirect competition from other drugs seeking to improve the underlying disorders leading to iron overload (described below).

Exhibit 4: Competitive environment (selected)

Drug	Company	Stage	Technology	Indication
Exjade (deferasirox)	Novartis	Marketed	Chelator	Iron overload
Jadenu (deferasirox)	Novartis	Marketed	Chelator	Iron overload
Desferal (deferoxamine mesylate)	Novartis	Marketed	Chelator	Iron overload
LJPC-401	La Jolla	Phase II	Hepcidin agonist	Iron overload
PTG-300	Protagonist	Phase II	Hepcidin agonist	Iron overload
IONIS-TMPRSS6-L_{RX}	Ionis	Phase I	TMPRSS6 antisense	Iron overload
VIT-2763	Vifor	Phase I	Ferroportin antagonist	Iron overload
Aranesp (darbepoetin alfa)	Amgen	Marketed	Erythropoietin receptor agonist	Anaemia
Epogen (epoetin alfa)	Amgen	Marketed	Erythropoietin receptor agonist	Anaemia
Reblozyl (luspatercept-aamt)	Acceleron	Marketed	TGF-beta inhibitor	Anaemia
Roxadustat	FibroGen	Phase III complete/ Approved in China and Japan	HIF prolyl hydrolase inhibitor	Anaemia
Vadadustat	Akebia	Phase III complete/ Submitted in Japan	HIF prolyl hydrolase inhibitor	Anaemia
Molidustat	Bayer	Phase III	HIF prolyl hydrolase inhibitor	Anaemia
Zynteglo	Bluebird	Phase III/ EMA conditional approval	Gene therapy	Beta-thalassemia
OTL-300	Orchard	Preclinical	Gene therapy	Beta-thalassemia
ST-400	Sangamo	Phase I/II	Gene therapy	Beta-thalassemia
CTX001	Crisper	Phase I/II	Gene therapy	Beta-thalassemia
Thalagen	EGT	Preclinical	Gene therapy	Beta-thalassemia

Source: Evaluate Pharma, company reports

Beta-thalassemia

Beta-thalassemia is a congenital blood disorder caused by reduced expression of the haemoglobin beta chain, leading to a reduced number of mature red blood cells, low haemoglobin levels and anaemia. Erythropoiesis is highly activated but ineffective, as these patients typically display a large proportion of immature blood cells (reticulocytes), which fail to mature into red blood cells (erythrocytes). However, this high level of erythropoiesis supresses hepcidin and causes high serum iron concentrations.

[3] Richard F, et al. (2019) First-in-human single- and multiple-ascending dose study of the oral ferroportin inhibitor vit-2763 in healthy subjects. *HemaSphere* 3, 205–206.

Genetic markers for the disease are common and approximately 1.5% of the world's population are carriers, although the rate of symptomatic individuals is substantially lower (one in 100,000 incidence).[4] The rates of the disease are higher in individuals of European decent (one in 10,000). The disease is roughly classed by its severity: major, intermedia and minor, with beta-thalassemia major being the most severe, occurring in approximately one-third of symptomatic cases (an estimated 23,000 new beta-thalassemia major cases worldwide per year).[5] Beta-thalassemia major presents in the first few years of life and requires lifelong blood transfusions. Approximately, another third of symptomatic patients (19,000) have what is called haemoglobin E beta-thalassemia, of which approximately half are transfusion dependent. Iron overload is generally the cause of death in these transfusion-dependent patients, although they can live to over 40 with strict adherence to chelation therapy. There are few other clinical options for transfusion-dependent patients, as other anti-anaemia treatments such as erythropoietin are ineffective in transfusion-dependent patients. Anti-anaemia drugs generally operate by stimulating erythropoiesis. Erythropoiesis is already activated in beta-thalassemia major, but red blood cell maturation is impaired, so these treatments are ineffective. The notable exception to this is the recently approved Reblozyl (luspatercept-aamt, Acceleron Pharma), which showed positive results in beta-thalassemia. However, it is worth noting that 79% of patients failed to show a response (33% reduction in transfusion burden).

However, there are several other new technologies in development that may have an impact on the potential market for iron overload treatment in this population. There are three programmes to our knowledge investigating gene therapy as a curative treatment for the disease. The most advanced, Zynteglo from Bluebird, is in Phase III clinical studies, and has conditional approval in Europe. In earlier studies the drug allowed 11 of 14 transfusion dependent patients to achieve transfusion independence for up to 56 months. However, a major drawback to this treatment is that it requires myeloablation to remove the mutated bone marrow before the therapy is administered. This procedure carries significant risk and we therefore expect the treatment to be limited to the most severe and most poorly controlled cases.

MDS

MDS is a haematologic disorder characterised by myelodysplasia (the aberrant maturation of blood cells in the bone marrow) and cytopenias, in particular red blood cells, and a variable risk of progression to acute myeloid leukemia (AML). Additionally, immature blood cells, called blasts, can accumulate in the bone marrow and begin to crowd out other cells. When the fraction of blasts in bone marrow rises to above 30% (20% according to WHO guidelines), the disease is officially considered AML as opposed to MDS. AML is characterised by the rapid accumulation of these blasts and the quick progression of the disease, whereas MDS is typically chronic and in many cases there is little risk of progressing to AML (depending on subtype).

Estimates of the incidence of MDS vary, but the consensus is that it is under-reported. Data from the US National Cancer Institute's screening programme, SEER, suggest an incidence of 4.1 to 4.6 per 100,000,[6] although data mining of medical records suggest higher rates of 5.3 to 13.1 per 100,000.[7] It is predominantly a disease of the elderly with 86% of new cases in patients over the age of 65. Patients with low-risk disease receive supportive case such as transfusions and may receive a course of chemotherapy, typically Vidaza (azacitidine) or Dacogen (decitabine), which can improve blood counts.

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4 Galanello R and Origa R (2010) Beta-thalassemia. *Orphnet J Rare Dis* 5, 11.

5 Weatherall DJ (2012) The definition and epidemiology of non-transfusion-dependent thalassemia. *Blood Rev* 26 suppl. 1, S3–S6.

6 Ma X (2012) Epidemiology of Myelodysplastic Syndromes. *Am J Med.* 125 suppl. 7, S2–S5.

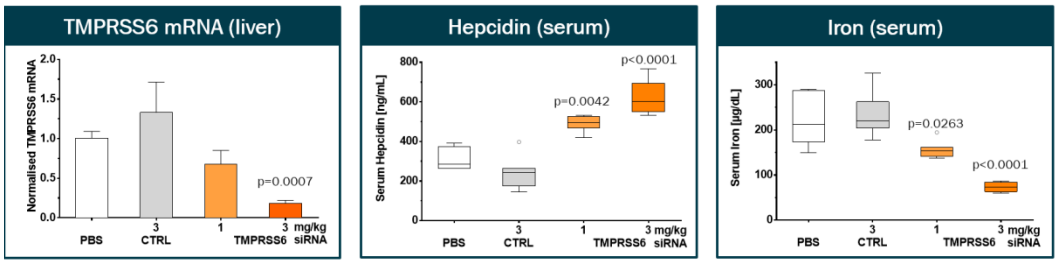
7 Cogle CR (2015) Incidence and Burden of the Myelodysplastic Syndromes. *Curr Hem Malig Rep* 10, 272–281.

The treatment of MDS is evolving quickly with the approval of new drugs to treat myeloid disorders such as Daurismo (glasdegib, Pfizer) and Venclexta (venetoclax, AbbVie) for AML (among other drugs). However, we expect these drugs to be largely limited to patients with aggressive forms of the disease. We expect SLN124 to be used predominantly in low-risk patients who are facing years of transfusions. Unlike beta-thalassemia, MDS patients can potentially be treated with a range of anti-anaemia drugs and recently both of the two new drugs, luspatercept and roxadustat, have been tested in MDS patients. The benefits from anaemia treatments have been limited historically: approximately 20% of patients who receive Epogen achieve a lower transfusion dependence. This is likely caused by impaired erythropoiesis in these patients, and it is unclear at this time if any of these new treatments may avoid this limitation.

Preclinical data

Silence has reported data suggesting that SLN124 is effective at knocking down TMPRSS6 and reducing serum iron in model systems. The company also demonstrated that the reduction in TMPRSS6, induction of hepcidin and suppression of serum iron are all dose dependent, which is highly supportive of the drug's activity (Exhibit 5). These data were collected in mouse models of HH, suggesting that the mechanism is not compromised in this setting. Separately, the company demonstrated that a single subcutaneous dose of SLN124 effectively reduced serum iron levels by approximately 50% for six weeks in mice (not depicted here).

Exhibit 5: SLN124 decreases serum iron in mice

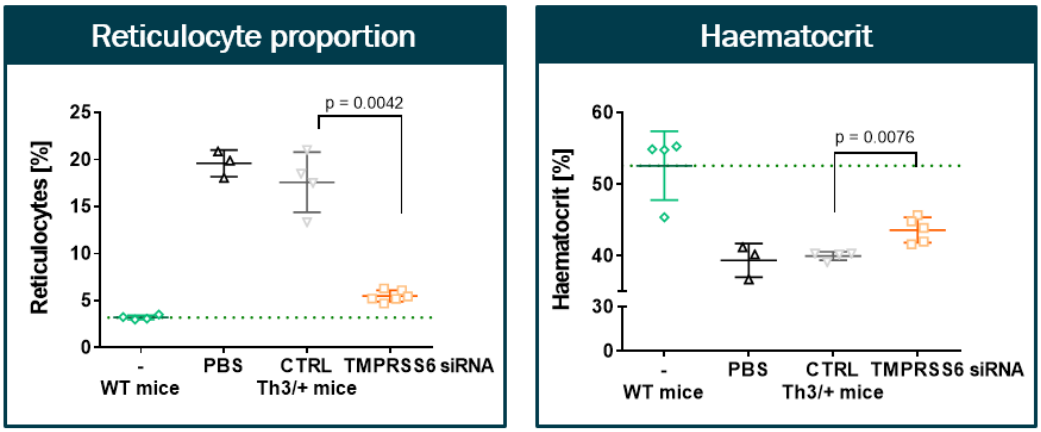


Source: Silence Therapeutics

An interesting finding was that in a model of beta-thalassemia intermedia SLN124 improved erythropoiesis in these mice by reducing the fraction of reticulocytes and improving haematocrit (a measure of the number of red blood cells). The reason behind this finding is not well understood, but is supported by the literature,[8] and some sources suggest it is likely due to reduced iron mediated toxicity and the reduction of reactive oxygen species.

[8] Nai A, et al. (2012) Deletion of TMPRSS6 attenuates the phenotype in a mouse model of β-thalassemia. *Blood* 119 5021–5029.

Exhibit 6: SLN124 improves erythropoiesis in mice



Source: Silence Therapeutics

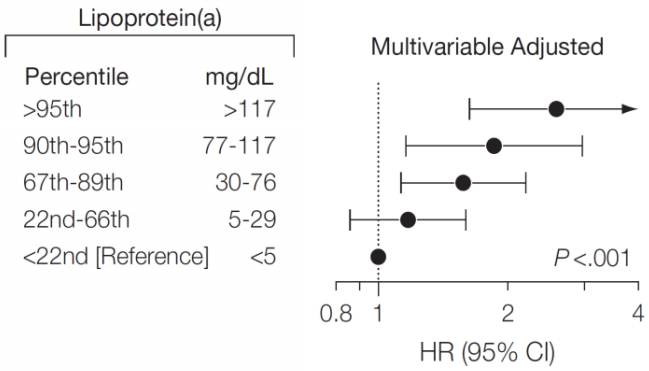
SLN360

The company has disclosed one additional development programme: SLN360 for the treatment of cardiovascular disease. SLN360 is an siRNA drug designed to reduce Lipoprotein(a) [Lp(a), pronounced 'L P little a'], which is a lipoprotein associated with poor cardiac outcomes. Lp(a) can be considered either a subtype of low-density lipoprotein (LDL) particles or a closely related species, and is similarly associated with atherosclerosis and other cardiovascular disease. Interestingly, Lp(a) concentrations vary dramatically between individuals by many orders of magnitude and appear to be almost entirely genetically controlled as they are unaffected by diet or exercise. Because of this, Lp(a) can be used as an independent genetic predictor of CV disease and is recommended for use as a diagnostic. It is an attractive target for knockdown, because many individuals have very low levels of Lp(a) with no apparent adverse effects. Moreover, Lp(a) is produced in the liver making it an appropriate target for Silence's platform.

The market for such a product is significant given the high underlying rates of CV disease. The CDC estimates that 28.2 million adults are currently diagnosed with CV disease in the US. We expect the product to be approved specifically for patients who have been identified as having high levels of Lp(a). The 90th percentile and higher of Lp(a) expressers have approximately 1.5x to 2x the risk of myocardial infarction as low expressers (Exhibit 7),[9] and have similar additional increased risks for stroke and aortic stenosis. Moreover, the currently available treatments are ineffective at controlling levels of Lp(a). Statins have a minimal effect on Lp(a) concentrations and although the newly approved PCSK9 inhibitors Repatha (evolocumab, Amgen) and Praluent (alirocumab, Regeneron/Sanofi) can reduce Lp(a) levels by up to 30%, this is unlikely to be sufficient to address the high Lp(a) expressers. For comparison, in preclinical studies performed in non-human primates, SLN360 was able to achieve over 90% reductions in Lp(a) levels (Exhibit 8).

[9] Kamstrup PR, et al. (2009) Genetically Elevated Lipoprotein(a) and Increased Risk of Myocardial Infarction. *J Am Med Assoc* 301, 2331–2339.

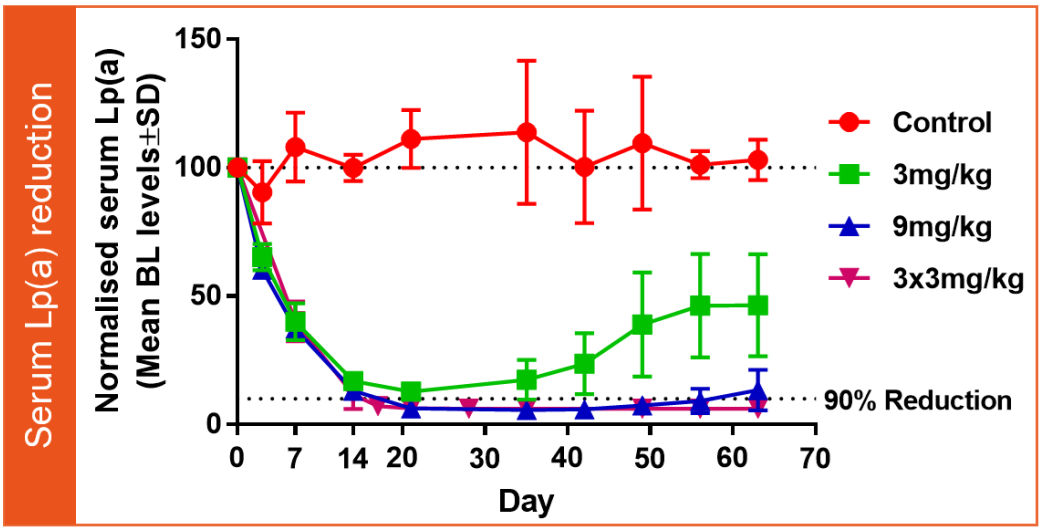
Exhibit 7: Risk of myocardan infarction as a function of Lp(a)



Source: Silence Therapeutics, adapted from Kamstrup et al.

One concern is that knocking down Lp(a) could adversely affect coagulation. The protein Apo(a) on Lp(a) shares a high degree of homology with plasminogen, which is important for breaking down and preventing blood clots (through its catalytically active cleavage product, plasmin). This moiety is known to bind to and inhibit platelets.[10] Moreover, Lp(a) is rich in the protein PAF-acetylhydrolase, which breaks down platelet activating factor (PAF).[11] Therefore, considering that Lp(a) has antithrombotic activity, the concern is that its knockdown will increase the rates of blood clots, although at this time the worry is purely hypothetical. The company is aware of this possibility and has carried out testing in vitro and in non-human primates to show that knockdown of Lp(a) does not affect plasminogen levels.

Exhibit 8: SLN360 preclinical data in non-human primates



Source: Silence Therapeutics

Other companies are also studying knockdown of Lp(a) for CV disease. Novartis exercised its option to license the Lp(a) antisense drug TQJ230 from Akcea and Ionis for $150m in February 2019 following positive Phase II results. Importantly from these results, effects on platelet counts were minimal. Amgen is also developing an Lp(a) targeting siRNA (AMG-890) in collaboration with Arrowhead Pharmaceuticals, which entered Phase I testing in 2018. Silence has stated that it plans to file an IND for SLN360 in H220.

[10] Exratty A, et al. (1993) Lipoprotein (a) binds to human platelets and attenuates plasminogen binding and activation. *Biochem* 32, 4628–4633.

[11] Tsironis LD, et al. (2004) Effect of lipoprotein (a) on platelet activation induced by platelet-activating factor: role of apolipoprotein (a) and endogenous PAF-acetylhydrolase. *Cariovasc Res* 63, 130–138.

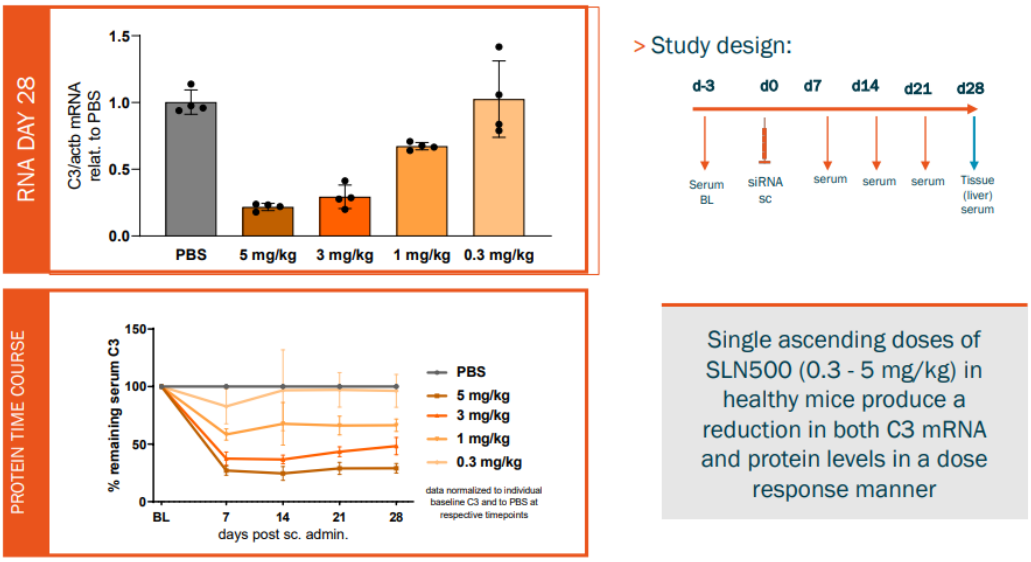
SLN500

Silence announced on 18 July 2019 that it had entered into an agreement with Mallinckrodt for the rights to its preclinical asset SLN500. SLN500 is an siRNA knockdown of the complement protein C3. Additionally, the deal included options for up to two other undisclosed targets in the complement system. Silence received an upfront payment of $20m and is responsible for development of SLN500 through preclinical development and a Phase I trial, although it is eligible for clinical and manufacturing financial support (Silence will pay for preclinical activities). Silence is eligible for up to $10m in research milestones for SLN500, the first $2m of which was announced on 23 September 2019. This milestone was delivered in relation to 'specific preclinical aspects' of the programme that had been completed. Each of the two other option assets is entitled to similar development milestones. The agreement also includes $100m in additional clinical and regulatory milestones (for SLN500) and $563m in commercial milestones (for SLN500). The company will receive tiered royalties on sales ranging from low double digits to high teens. The agreement also includes up to $703m in additional milestones for each additional optioned asset. Finally, Mallinckrodt made a $5m equity investment in Silence (approximately 5m shares at 79p) and will have a seat on the board. We view these as especially favourable terms to Silence, as the upfront and royalties are high for drugs licensed at this stage. Moreover, there is little financial risk to Silence considering it must only pay for activities up to preclinical toxicology. Mallinckrodt has recently come under scrutiny regarding its association with the opioid crisis and financial risks associated with these liabilities. We believe that it is too early to draw any conclusions regarding the ability of Mallinckrodt to service this agreement, but if the programme is successful, there will likely be other willing partners. The company has stated that it is targeting filing an IND in 2021.

The complement system is an integral part of the body's immune system and one of the body's primary mechanisms to kill pathogens. The system consists of a series of proteins that interact in an amplifying cascade of signals in response to antibody binding or an innate immune response. The complement cascade is directly cytotoxic and results in the assembly of pore-forming complexes in the membrane of the pathogen, the so-called membrane attack complex (MAC), leading to lysis. Additionally, binding of complement factors to the surface of pathogens can induce them to cluster and stick together, improving their identification and clearance from the body. The target of SLN500, C3, is secreted by the liver, making the protein an attractive target for the company's platform.

Dysregulation of the complement system is implicated in a number of disorders. The most serious of these are hemolytic disorders in which the complement system attacks circulating blood cells leading to anemia and blood clots. These disorders include paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). Both are rare diseases, typically genetic in origin, where the normal regulatory mechanisms that allow the complement system to recognise the patient's own cells are lost. Currently the only available treatment for these disorders is Soliris (eculizumab; Alexion), an inhibitor of the complement enzyme C5. Additionally, the complement system can be implicated in a range of other disorders, either directly (as in the case of hereditary angioedema), or indirectly as a result of underlying antibody mediated disease (as in the case for myasthenia gravis). Lead optimisation is still underway, but the company has published some proof of mechanism data showing knockdown in mice (Exhibit 9).

Exhibit 9: SLN500 preclinical data



Source: Silence Therapeutics

Although the company has not announced which indications will be targeted, we can say that there is significant competition in the complement disorder space: there are over a dozen ongoing clinical programmes targeting PNH alone. Alnylam currently has an RNAi therapy (cemdisiran) that it is examining for a range of complement disorders that is currently in Phase II. Alexion has also announced a collaboration with Dicerna to develop RNAi drugs to treat complement disorders, as a follow-on strategy to Soliris.

Moreover, there has been substantial interest recently in the licensing of drugs targeting the complement system. It was announced in October 2019 that UCB would acquire Ra Pharma to acquire its C5 complement drug, in a transaction valued at $2.1bn. Additionally, Alexion announced in October 2019 that it would acquire Achillion for $930m. Achillion is developing a small molecule inhibitor of Factor D, which could potentially be used as an alternative to Alexion's injectable Soliris.

Takeda project

The company announced on 7 January 2020 that it entered into a 'technology evaluation agreement' with Takeda to develop a drug for an undisclosed target identified by Takeda. The companies also did not disclose the indication that the drug will be developed to treat. As part of the deal Takeda agreed to provide research funding to Silence in the order of single-digit millions of US dollars. Additional details of the agreement were undisclosed, but the companies did agree to negotiate licensing terms in the future if the collaboration proves successful.

This development agreement with a major pharmaceutical company further demonstrates that the company's technology can withstand the scrutiny of some of the most important players in the pharmaceutical business.

Royalty streams

Silence has several additional potential revenue streams through licensing agreements. In 2005 it licensed its AtuRNAi technology to Quark, which developed QPI-1002, a knockdown of p53. The programme is in two Phase III studies for patients with acute kidney injury and the prevention of delayed graft function in kidney transplant recipients. P53 is a key mediator of apoptosis (cell death)

and by knocking it down, presumably cells would be less likely to die when exposed to the stress of kidney injury or transplant. Quark previously reported positive clinical results for the AKI programme, although the graft function programme failed to meet its primary endpoints in Phase II. Novartis has the exclusive option to license the programme in exchange for royalties and up to $670m in milestone payments. Silence is entitled to either 1.5–4% royalties plus milestones, or 15% of the royalties and milestones payable to Quark from Novartis in the event it takes the option. The drug would be taken prophylactically following cardiac surgery or kidney transplant, of which there are over half a million per year and 14,000 per year, respectively.

Additionally, the company is entitled to royalties (0.33–1.0%) on EU sales of Onpattro as part of its settlement agreement with Alnylam through 2023. Onpattro is approved for the treatment of hATTR amyloidosis, a disease with a worldwide prevalence of 50,000.[12] The product is priced at approximately $450,000 per year in the US, although pricing negotiations are ongoing in Europe. NICE agreed to reimburse the drug at £300,000.

Sensitivities

The immediate challenges faced by Silence Therapeutics are similar to other early stage drug development companies, but have several unique qualities. Although the company has immediate plans to enter the clinic, at this time the support for its programmes is almost entirely based on animal data. There are no guarantees that its products will behave similarly in humans, although the particular balance of risks to RNAi development are different than those for small molecule or antibody based therapeutics. All of the genes that the company is targeting are expressed in the liver and the company's targeting technology using GalNAc is well established at this point to drive liver targeting. It is unlikely that changes to the nucleotide sequences in its products will dramatically affect the targeting or distribution of its drugs. However, RNAi therapeutics can have significantly different potencies and achieve variable levels of knockdown of their genetic targets; at this time it is unknown how potent the constructs being investigated are. Moreover, it is difficult to have an accurate assessment of potency before human testing. Given that the mechanisms underlying these therapies are relatively well understood, we expect initial readouts of activity to be highly predictive of eventual efficacy.

We expect the company to face significant competition both during the eventual commercialisation of these products as well as for partners to advance these programmes. There are a large number of other treatments that are competing both directly and indirectly, including assets developed by much larger companies with greater resources. Moreover, Silence's programmes are unlikely to be first-in-class in any instance. Silence will likely need to secure partners to advance its clinical programmes, especially for SLN360 because it is likely to require a major cardiac outcomes study that is beyond the scope of anything other than a major pharmaceutical company can accomplish. Any partnerships may offset any future financing risk faced by Silence, which is also significant. We expect the company to require £105m in additional capital to reach profitability.

Valuation

We arrive at an initial valuation of £345m or 440p per share based on a risk-adjusted NPV analysis and a 12.5% discount rate (our standard for precommercial products). SLN124 is the highest value asset at £141m. We assume the drug will achieve lower penetration in MDS (15%) compared to beta-thalassemia (20%) due to the availability of more treatment options. However, we expect

[12] Gertz MA (2017) Hereditary ATTR Amyloidosis: Burden of Illness and Diagnostic Challenges. *Am J Manag Care* 23, S0

genetic therapies to be successfully developed that address beta-thalassemia, and we forecast 25% of transfusion dependent patients to achieve transfusion independence via these therapies by 2037. We assume pricing of $234,000 in the US and $117,000 in Europe before gross to net discounts of 20%. We expect the company to perform separate trials for beta-thalassemia and MDS following the initial combined Phase I. We expect these programmes to require 248 patients for MDS and 68 for beta-thalassemia (fewer patients due to the rareness of the disease) at an expense of $100,000 apiece. Our valuation includes COGS of 12% and marketing costs of 10%, with $10m overhead. We expect the product to be protected by biologic exclusivity in the US (12 years) and Europe (10 years). We assign a probability of success for the programme of 15% because our assessment of the product to this point is based purely on preclinical data. This probability is typical for assets entering Phase I.

We model the initial market for SLN360 as patients with a prior diagnosis of CV disease and Lp(a) expression levels in the 90th percentile or higher. We model pricing similar to Praluent, which recently underwent a 60% price cut in the US to approximately $6,000 per year of treatment and is currently priced at approximately $4,000 in Europe, and we model a 2% annual price increase. We expect there to be significant competition in the space with other CV drugs and other Lp(a) drugs potentially, and model the product capturing 10% of the market. We also expect this competition to translate into higher marketing costs for the product, which we model at 20%. Otherwise our operational assumptions are similar to SLN124. The major hurdle for this product is that approval will likely require a very large Phase III cardiovascular outcomes study, which we expect to include approximately 20,000 patients, similar to other trials used to support the approval of Repatha and Praluent. We expect this study to be beyond the scope of what Silence can accomplish without a large pharmaceutical partner, but it is included in the calculation of the drug's value. Our probability of success is 5%, which reflects that the product is still in preclinical testing, with an IND filing expected in H220.

Although the target indication has not been announced, we include some aspects of the SLN500 development agreement in our model. A large portion of this valuation (£26.4m) is driven by the remaining $8m research milestones payable, we assume at the end of Phase I, with the remainder attributed to potential royalties and future milestones. In the absence of the target indication, we are using a hypothetical product with $400m in peak sales as a placeholder and include $400m in additional milestones. We assign a 5% probability of success, which is our standard for assets with significant preclinical work to be done. We model the product entering the clinic in 2021.

We also include the development project with Takeda in our valuation using a placeholder model similar to that described for SLN500. In the case of the Takeda project, we assume a lower probability of success (3%) because the programme is still in the feasibility testing stage. Additionally, we expect the project to enter the clinic later (in 2022). Otherwise the model is similar to SLN500 as we are using details from that agreement as a basis for future agreements: $400m peak sales as a placeholder, 11–19% royalties, and the same milestones ($8m development and $400m commercial).

We also include royalty streams from Onpattro (Europe only) and QPI-1002. For the former, we assume current pricing of £300,000 (based on the NICE decision) and 10% market share. We assume QPI-1002 will face pricing pressure as we expect it to be included in the diagnosis-related group (DRG) pricing bundles, and we assume a launch price of $2,200 per procedure.

Exhibit 10: Valuation of Silence Therapeutics

Product	Indication	Clinical stage	Prob. of success	Launch year	Peak sales ($m)	Margin/ royalty rate	rNPV (£m)
SLN124	Beta-Thalassemia	Phase I ready	15%	2026	489.2	59%	69.1
	MDS	Phase I ready	15%	2026	683.7	60%	72.1
SLN360	Cardiovascular disease	Preclinical	5%	2028	5,214.0	54%	111.5
SLN500	Complement disorder	Preclinical	5%	2027	*400	*11–19%	26.4
Takeda project	Undisclosed	Preclinical	3%	2028	*400	*11–19%	17.7
QPI-1002	AKI & Kidney Transplant	Phase III	60%	2022	381.5	1.5–4.0%	9.7
Onpattro	hATTR Amyloidosis	Approved			**361.6	0.33–1.0%	4.8
Total							311.5
Net cash and deposits (at 31 December 2019) (£m)							33.5
Total firm value (£m)							345.0
Total basic shares (m)							78.4
Value per basic share (p)							440
Dilutive options (m)							4.7
Total diluted shares (m)							83.1
Value per diluted share (p)							419

Source: Silence Therapeutics reports, Edison Investment Research. Note: *Peak sales for SLN500 and Takeda are a placeholder, royalty rates described as 'low double digit to high teens' for SLN500. **European sales estimates before 2023 only.

Financials

Silence reported an operating loss of £20.6m for 2018, roughly split between administrative expenses and R&D, and results for H119 were largely in line (£5.1m R&D spend and £4.7m administrative spend). We expect R&D expenses to have expanded in 2019 to £12.6m (from £9.7m), but for this to have been offset by reduced administrative expenses (£8.4m from £10.8m, due to the conclusion of litigation) and cash from the recently signed Mallinckrodt deal. This increase in R&D is associated with the advancement of the company's clinical programmes and preparations for the initiation of the SLN124 Phase I clinical study in Q120.

Our 2019 and 2020 revenue estimates are largely dependent on how the payments from Mallinckrodt and Takeda are recognized and deferred and may change based on company accounting. We recognize the $2m Mallinckrodt milestone in 2019 and defer the $20m upfront into 2020 and beyond ($6m recognized in 2020). We recognize $2m from the $5m Takeda research payment in 2020 and the rest is deferred.

The company has reported that it ended 2019 with £33.5m in cash. We expect the company to require an additional £105m in financing to reach profitability in 2026, which we include as illustrative debt (£30m in 2021, £30m in 2022, £45m in 2024). These costs include Phase I and Phase II studies for SLN360, although we expect the company to require a large pharmaceutical partner to further advance the programme in the clinic, and we expect a portion of this financing requirement to be met through such an agreement.

Exhibit 11: Financial summary

£'000s	2017	2018	2019e	2020e
31-December	IFRS	IFRS	IFRS	IFRS
INCOME STATEMENT				
Revenue	16.0	0.0	2,147.1	5,799.8
Cost of Sales	0.0	0.0	0.0	0.0
Gross Profit	16.0	0.0	2,147.1	5,799.8
R&D	(7,943.0)	(9,743.0)	(12,663.0)	(20,031.6)
SG&A	(6,464.0)	(10,828.0)	(8,377.2)	(8,628.5)
EBITDA	(13,958.0)	(20,172.0)	(18,474.1)	(22,481.3)
Normalised operating profit	(13,753.0)	(19,890.0)	(18,191.7)	(22,137.8)
Depreciation & amortisation	(433.0)	(399.0)	(419.0)	(379.0)
Exceptionals	0.0	0.0	0.0	0.0
Share-based payments	(638.0)	(681.0)	(701.4)	(722.5)
Reported operating profit	(14,391.0)	(20,571.0)	(18,893.1)	(22,860.3)
Net Interest	206.0	45.0	0.0	0.0
Joint ventures & associates (post tax)	0.0	0.0	0.0	0.0
Exceptionals	10,410.0	0.0	0.0	0.0
Profit Before Tax (norm)	(13,547.0)	(19,845.0)	(18,191.7)	(22,137.8)
Profit Before Tax (reported)	(3,775.0)	(20,526.0)	(18,893.1)	(22,860.3)
Reported tax	2,157.0	2,115.0	3,748.9	4,348.4
Profit After Tax (norm)	(5,806.4)	(17,800.2)	(16,317.2)	(19,856.8)
Profit After Tax (reported)	(1,618.0)	(18,411.0)	(15,144.2)	(18,511.9)
Minority interests	0.0	0.0	0.0	0.0
Discontinued operations	(1,306.0)	0.0	0.0	0.0
Foreign exchange adjustment	404.0	94.0	0.0	0.0
Net income (normalised)	(5,402.4)	(17,706.2)	(16,317.2)	(19,856.8)
Net income (reported)	(2,520.0)	(18,317.0)	(15,144.2)	(18,511.9)
Basic average number of shares outstanding (m)	70	70	78	82
EPS - basic normalised (p)	(7.72)	(25.18)	(20.83)	(24.15)
EPS - diluted normalised (p)	(7.72)	(25.18)	(20.83)	(24.15)
EPS - basic reported (p)	(2.31)	(26.18)	(19.34)	(22.51)
Dividend (p)	0.00	0.00	0.00	0.00
BALANCE SHEET				
Fixed Assets	9,460.0	9,387.0	9,157.5	8,968.0
Intangible Assets	8,057.0	8,191.0	8,151.0	8,151.0
Tangible Assets	1,170.0	921.0	731.5	542.0
Investments & other	233.0	275.0	275.0	275.0
Current Assets	45,547.0	29,498.0	36,512.3	18,412.8
Stocks	0.0	0.0	0.0	0.0
Debtors	733.0	0.0	0.0	0.0
Cash, cash equivalents, and deposits	42,745.0	26,494.0	33,508.3	15,408.8
Other	2,069.0	3,004.0	3,004.0	3,004.0
Current Liabilities	(2,657.0)	(3,830.0)	(5,129.4)	(5,436.2)
Creditors	(2,657.0)	(3,830.0)	(5,129.4)	(5,436.2)
Tax and social security	0.0	0.0	0.0	0.0
Short term borrowings	0.0	0.0	0.0	0.0
Other	0.0	0.0	0.0	0.0
Long Term Liabilities	0.0	0.0	(16,129.0)	(15,322.6)
Long term borrowings	0.0	0.0	0.0	0.0
Other long term liabilities	0.0	0.0	(16,129.0)	(15,322.6)
Net Assets	52,350.0	35,055.0	24,411.4	6,622.0
Minority interests	0.0	0.0	0.0	0.0
Shareholders' equity	52,350.0	35,055.0	24,411.4	6,622.0
CASH FLOW				
Op Cash Flow before WC and tax	(13,320.0)	(19,491.0)	(17,772.7)	(21,758.8)
Working capital	1,711.0	913.0	1,299.4	306.8
Exceptional & other	3.0	6.0	16,129.0	(806.5)
Tax	2,007.0	1,812.0	3,748.9	4,348.4
Net operating cash flow	(9,599.0)	(16,760.0)	3,404.6	(17,910.0)
Capex	(173.0)	(188.0)	(189.5)	(189.5)
Acquisitions/disposals	0.0	0.0	0.0	0.0
Net interest	(15.0)	39.0	0.0	0.0
Equity financing	48.0	341.0	3,799.2	0.0
Dividends	0.0	0.0	0.0	0.0
Other	13,202.0	319.0	0.0	0.0
Net Cash Flow	3,463.0	(16,249.0)	7,014.3	(18,099.5)
Opening net debt/(cash)	(39,012.0)	(42,745.0)	(26,494.0)	(33,508.3)
FX	270.0	(2.0)	0.0	0.0
Other non-cash movements	0.0	0.0	0.0	0.0
Closing net debt/(cash)	(42,745.0)	(26,494.0)	(33,508.3)	(15,408.8)

Source: Company accounts, Edison Investment Research

Contact details	Revenue by geography
72 Hammersmith Road London, W14 8TH UK +44 (0)20 3457 6900 www.silence-therapeutics.com	N/A

Management team

Executive chairman and acting CEO: Iain Ross

Iain has over 40 years' experience in the international life sciences and technology sectors, where he has completed multiple financing transactions, and over 25 years in cross-border management as chairman and CEO. Currently he is non-executive chairman of Redx Pharma plc (LSE), e-Therapeutics plc, and Kazia Therapeutics Limited (ASX and NASDAQ) He has advised banks and private equity groups on numerous company turnarounds including, as CEO of Quadrant Healthcare (1996–2000), taking the company public and signing numerous collaborations before selling the business to Elan in 2001. As chairman and CEO at Allergy Therapeutics (2001–02) he restructured the company prior to its IPO, and as chairman at Silence Therapeutics plc (2004–10) he turned the business around through M&A and established numerous big pharma collaborations. As executive chairman at Ark Therapeutics plc (2010–15) he successfully restructured the business and disposed of the manufacturing assets and reversed in Premier Veterinary Group.

CFO: Dr Rob Quinn

Rob was appointed chief financial officer and company secretary of Silence in January 2019. He holds a PhD in biochemistry from the University of Manchester and is a qualified chartered accountant. Following his PhD, Rob trained as an accountant at Deloitte before joining GlaxoSmithKline (2013–17), with time spent working in internal audit, M&A and commercial finance. Rob's last role at GSK was as area finance director for the Africa & Developing Countries business unit, covering sales of pharmaceuticals and vaccines to over 45 countries. Rob joined Silence in April 2017 as head of financial planning and analysis before broadening his responsibilities to legal, IT and manufacturing.

Head of R&D and CMO: Dr Giles Campion

Giles is an expert in translational medicine and a highly experienced biotech and pharmaceutical professional across all therapeutic areas, most recently in orphan neuromuscular disorders. He has held senior global R&D roles in large pharmaceutical, diagnostics and biotech companies, including responsibility at board level. He served as chief medical officer and senior vice-president of R&D at Prosensa from 2009 to 2016, during which time the company signed a collaborative agreement with GSK worth up to $680m with double-digit royalties on product sales and co-commercialisation rights in certain territories. Prosensa went on to list on Nasdaq in 2013, raising $89.7m in an offering nine times oversubscribed, and was eventually acquired by BioMarin in 2015 for $680m.

VP, Head of Business Development: Dr John Strafford

John was appointed vice president, head of business development for Silence in May 2019. He has broad experience in biotech, management consulting and specialty pharma and has a track record in identifying strategic business opportunities and delivering significant commercial value for biotech growth. At Concordia International, a global specialty pharmaceutical company with over $600m in revenues, he was responsible for the end-to-end business development process and played a key role in the development of robust portfolio management processes, accelerating the identification of new product opportunities and driving pipeline value growth.

Principal shareholders	(%)
Richard Griffiths	23.78
Robert Keith	15.70
Lombard Odier Asset Mgt	12.08
Robert Quested	11.32
SG Securities	9.93
Mallinckrodt	6.46
Ali Mortazavi	2.62
D H Richardson	2.56
SpreadEx	1.71

Companies named in this report

AbbVie (ABBV), Acceleron (XLRN), Akcea (AKCA), Alexion (ALXN), Alnylam (ALNY), Ionis (IONS), La Jolla (LJPC), Mallinckrodt (MNK), Novartis (NVS), Pfizer (PFE), Protagonist (PTGX), Regeneron (REGN), Sanofi (SNY), Vifor (GNHAF).

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