New Data from SLN124 Healthy Volunteer Study Reinforce Broad Therapeutic Potential in Hematological Diseases

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- D ata presented at 202 1 ASH annual meeting showed d urable reductions in serum iron and transferrin saturation , strong safety profile and long duration of action
- Data s upport ongoing studies in patients with thalassemia and myelodysplastic syndrome and a new planned study in polycythemia vera

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LONDON, Silence Therapeutics plc, Nasdaq: SLN ("Silence" or "the Company"), a leader in the discovery, development and delivery of novel short interfering ribonucleic acid (siRNA) therapeutics for the treatment of diseases with significant unmet medical need, today presented additional positive data from the SLN124 healthy volunteer study at the 2021 American Society of Hematology (ASH) Annual Meeting in Atlanta, Georgia (USA). SLN124, a siRNA targeting the liver expressed TMPRSS6 gene, is currently in development for iron loading anemia conditions, thalassemia and myelodysplastic syndrome (MDS).

The phase 1, randomized, double-blind, placebo-controlled, single-ascending dose study evaluated the safety and tolerability of SLN124 (1.0, 3.0 and 4.5 mg/kg doses) in 24 healthy volunteers. Pharmacokinetic parameters and pharmacodynamic biomarkers of iron metabolism were also measured to assess reduction in iron.

Giles Campion, M.D., EVP, Chief Medical Officer and Head of Research & Development at Silence, said: "We developed our proprietary mRNAi GOLD™ platform with the focus on delivering targeted, precision medicines for

many diseases that lack effective treatments.The healthy volunteer study represents the first clinical data from our platform and demonstrated our ability to translate strong preclinical results in humans. By modulating endogenous hepcidin in a highly controlled manner,we believe SLN124 has the potential to address the needs of patients in a broad range of hematological diseases. We look forward to data from the ongoing studies in patients with thalassemia and MDS anticipated in the third quarter of next year."

Lead author, John Porter, M.D ., Professor and Consultant Hematologist , Red Cell Disorders Unit, University College London and University of College London Hospitals , commented: "Silencing the TMPRSS6 gene represents a new and promising therapeutic approach to manipulating hepcidin, which in turn has the potential to control a number of hematological conditions. I look forward to further development of SLN124 in people with iron-loading anemias, who could positively benefit from the effects we've seen in healthy volunteers."

New data presented at ASH today showed SLN124 was rapidly distributed (median tmax was 4.0 or 5.0 hours) and largely eliminated from plasma within 24 hours post-dose in all dosing groups. SLN124 plasma concentrations increased in a greater than dose-linear fashion between dosing groups.

Dose-related increases in circulating hepcidin, a key endogenous regulator of iron balance and distribution, were evident by Day 8; all doses resulted in sustained increments throughout the period of the study consistent with robust target engagement and TMPRSS6 gene knockdown. SLN124 induced durable reductions in serum iron; percentage change from baseline was ~50% at Day 29 with 3.0 and 4.5 mg/kg doses.

All SLN124 doses induced marked reductions in transferrin saturation (TSAT); absolute levels of TSAT achieved (10–16%) are below the level (< 20%) where iron availability to tissue is restricted and at or below that (< 16%) required to support normal erythropoiesis in health.

As previously reported, results showed all doses of SLN124 were well-tolerated with no serious or severe treatment emergent adverse events (TEAEs) or TEAEs leading to withdrawal. TEAEs did not appear to be dose dependent and the majority were mild, including transient injection site reactions which resolved without intervention.

The poster entitled, "SLN124 a GalNAc Conjugated 19-mer Double Stranded siRNA Reduces Iron and Increases Hepcidin Levels of Healthy Volunteers in a Phase 1 Clinical Study," is **available here**.

SLN124 is being evaluated in two phase 1 single-ascending dose studies in patients with thalassemia and MDS. SLN124 has Orphan Drug Designation for both conditions and rare pediatric disease designation for beta thalassemia. Silence plans to initiate a phase 1 study of SLN124 in polycythemia vera in the second half of 2022.

Enquiries:

Silence Therapeutics plc
Gem Hopkins, Head of IR and Corporate Communications
ir@silence-therapeutics.com
Tel: +1 (646) 637-3208

European P R
Consilium Strategic Communications
Mary-Jane Elliott/ Angela Gray / Chris Welsh
silencetherapeutics@consilium-comms.com
Tel: +44 (0) 20 3709 5700

US Media Relations
MKC STRATEGIES, LLC
Mary Conway
MConway@MKCStrategies.com
Tel: +1 (516) 606-6545

About Thalassemia and Myelodysplastic Syndrome (MDS)

Thalassemia and MDS are both rare diseases that prevent a person from producing enough healthy red blood cells. Low levels of healthy red blood cells, known as anemia, result in less oxygen being delivered to different parts of the body. This can cause symptoms such as excessive tiredness and weakness. It can also lead to other serious health problems, such as heart disease. People living with thalassemia or MDS can also store too much iron in their bodies, leading to a phenomenon called 'iron overload', which can damage organs such as the liver, heart and the endocrine system.

Both conditions are often treated with repeated blood transfusions, which add to the problem of iron overload. Iron chelation therapy removes excess iron from the body using special medicines. While it helps reduce the amount of body iron for people with thalassemia or MDS, it does not treat the underlying cause of the anemia or stop this from progressing. There is, therefore, a need for therapies that directly address the biological drivers of the anemia.

About Polycythemia Vera (PV)

PV is a rare blood cancer and one of a related group known as "myeloproliferative neoplasms" (MPNs). Unlike in thalassemia and MDS where the body does not produce enough red blood cells, people with PV produce too many red blood cells. This makes the blood thicker and less able to travel around the body, causing a variety of issues ranging from headaches and dizziness to more serious complications, such as blood clots.

Current treatments are focused on treating the symptoms of PV to reduce the number of red blood cells and reduce the risk of blood clots. They do not target the underlying genetic cause of the disease.

About SLN124

SLN124 is a gene ‘silencing’ therapy – one that is designed to temporarily block a specific gene’s message that would otherwise trigger an unwanted effect. In this case, SLN124 aims to temporarily ‘silence’ TMPRSS6, a gene that prevents the liver from producing a central regulator of iron balance and distribution in the body – hepcidin. Silencing TMPRSS6 by SLN124 increases endogenous hepcidin, with potential beneficial effects in several hematological disorders. SLN124 has demonstrated safety and proof-of-mechanism in a healthy volunteer study and is currently being studied in patients with thalassemia and MDS. SLN124 has orphan drug designation for both conditions and rare pediatric disease designation for beta thalassemia. Silence plans to initiate a phase 1 study of SLN124 in polycythemia vera in the second half of 2022.

About Silence Therapeutics

Silence Therapeutics is developing a new generation of medicines by harnessing the body's natural mechanism of RNA interference, or RNAi, to inhibit the expression of specific target genes thought to play a role in the pathology of diseases with significant unmet need. Silence's proprietary mRNAi GOLD™ platform can be used to create siRNAs (short interfering RNAs) that precisely target and silence disease-associated genes in the liver, which represents a substantial opportunity. Silence's wholly owned product candidates include SLN360 designed to address the high and prevalent unmet medical need in reducing cardiovascular risk in people born with high levels of lipoprotein(a) and SLN124 designed to address rare hematological diseases. Silence also maintains ongoing research and development collaborations with AstraZeneca, Mallinckrodt Pharmaceuticals, and Hansoh Pharma, among others. For more information, please visit **https://www.silence-therapeutics.com/**.

Forward-Looking Statements

Certain statements made in this announcement are forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995 and other securities laws, including with respect to the Company’s clinical and commercial prospects and the anticipated timing of data reports from the Company’s clinical trials. These forward-looking statements are not historical facts but rather are based on the Company's current expectations, estimates, and projections about its industry; its beliefs; and assumptions. Words such as 'anticipates,' 'expects,' 'intends,' 'plans,' 'believes,' 'seeks,' 'estimates,' and similar expressions are intended to identify forward-looking statements. These statements are not guarantees of future performance and are subject to known and unknown risks, uncertainties, and other factors, some of which are beyond the Company's control, are difficult to predict, and could cause actual results to differ materially from those expressed or forecasted in the forward-looking statements, including those risks identified in the Company’s most recent Admission Document and its amended Annual Report on Form 20-F filed with the U.S. Securities and Exchange Commission on April 29, 2021. The Company cautions security holders and prospective security holders not to place undue reliance on these forward-looking statements, which reflect the view of the Company only as of the date of this announcement. The

forward-looking statements made in this announcement relate only to events as of the date on which the statements are made. The Company will not undertake any obligation to release publicly any revisions or updates to these forward-looking statements to reflect events, circumstances, or unanticipated events occurring after the date of this announcement except as required by law or by any appropriate regulatory authority.

Source: Silence Therapeutics plc