SILENCE THERAPEUTICS

Corporate Presentation

September 2026

Forward-Looking Statements

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Silencing diseases through precision engineered medicines created with proprietary siRNA technology

Silence – siRNA Platform Company with Compelling Clinical Data Across Multiple Programs

mRNAi GOLD™ PLATFORM

- Proven GalNAc siRNA technology with broad utility
- Potent, durable and highly specific gene silencing
- Infrequent dosing enabled by durable pharmacology
- Strong and growing IP portfolio

CLINICAL RESULTS

- Four clinical-stage assets targeting large unmet needs in rare and cardiometabolic diseases
- Compelling clinical data generated across multiple programs

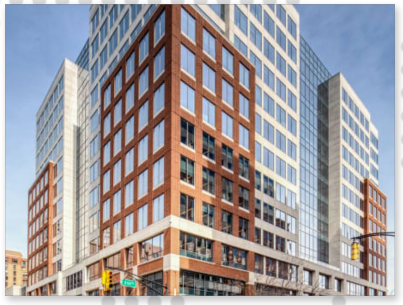
FRANCHISE OPPORTUNITY

- Divesiran: first-in-class siRNA for PV
- ~150K U.S. / ~3.5M global PV population[1]
- Potential best-in-class profile
- Additional pipeline opportunities beyond PV

Strong financial position with cash runway expected into 2029 to fund multiple catalysts

1. Using 44/100,000 global population: 7,800m, Kattamis, A. et al. Eur J Haematol (2020)

Our Global Footprint



NEW JERSEY
US OFFICE

LONDON
COMPANY HQ

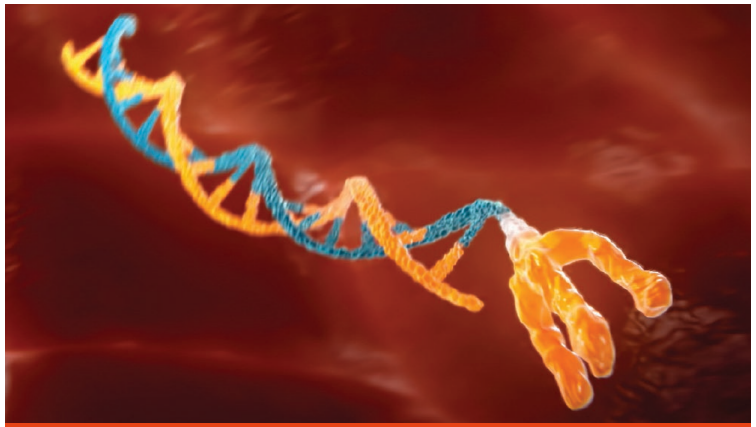
BERLIN
R&D OPERATIONS

siRNA expertise spanning drug discovery, design and clinical development

Our Toolbox Considers all Elements of siRNA and Ligand Design

siRNA molecule

- siRNA matched to target gene
- Silence has developed chemical modification patterns that enhance stability and improve activity



Linker

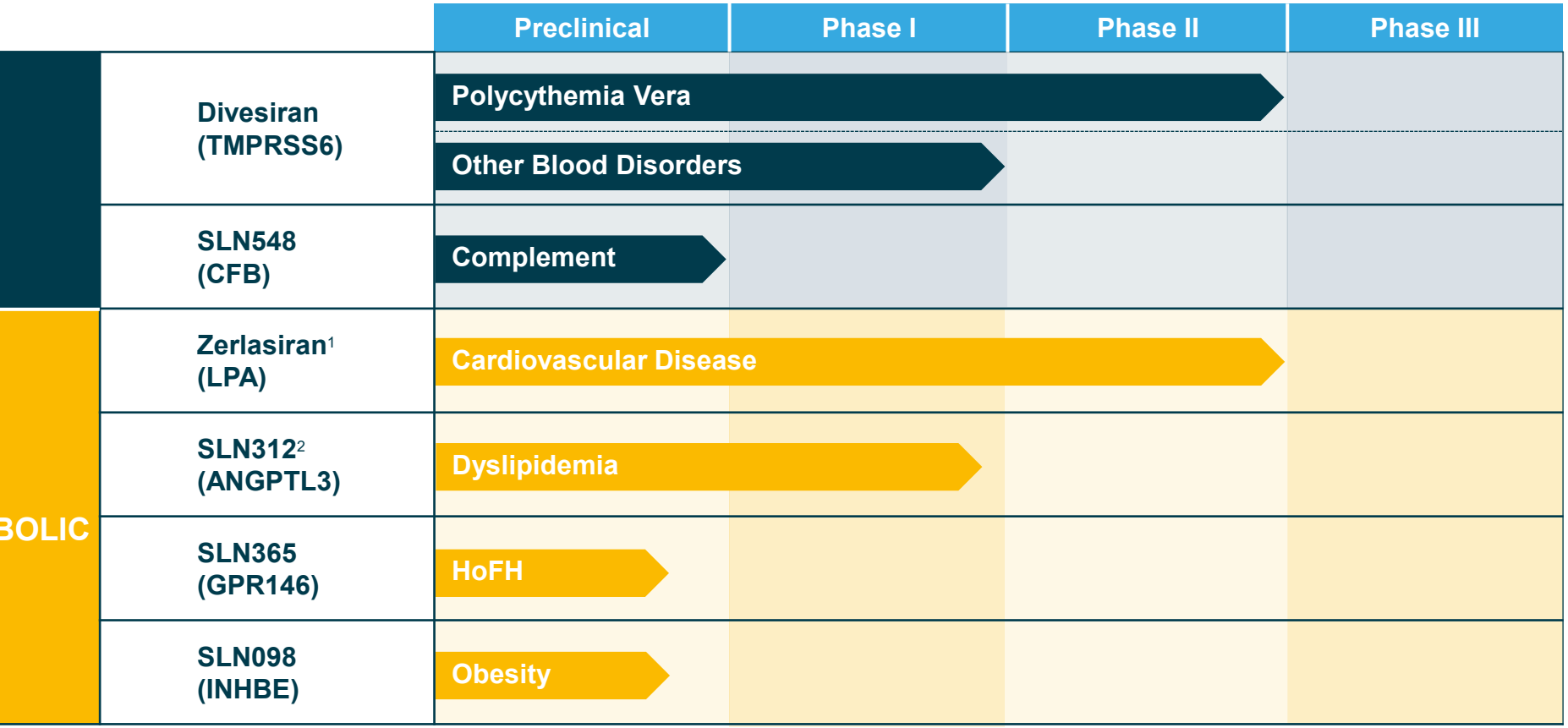
- Silence has developed proprietary linkers, enabling the attachment of targeting ligands to the siRNA molecule

GalNAc Ligand (delivery tool)

- GalNAc ligand delivers siRNA specifically to hepatocytes in the liver

Continuous Fine-Tuning to Further Improve Performance

Development Pipeline of siRNA Therapies



1. Zerlasiran is a Phase 3 ready asset; program well positioned for a potential third-party partner to advance development; 2. SLN312 is currently licensed to AstraZeneca. As announced in a Company press release dated March 5, 2026, Silence will re-gain exclusive rights globally to SLN312 following Phase 1; HoFH=Homozygous familial hypercholesterolemia

Rare Disease

Divesiran (TMPRSS6)

Polycythemia Vera (PV) is a Rare Blood Cancer with Significant Unmet Needs

- **Myeloproliferative neoplasm characterized by the excessive production of red blood cells (RBCs)**
  - Elevated hematocrit (HCT) is a hallmark of the disease, indicating overproduction of RBCs
  - Associated with JAK2 gain-of-function driver mutation in hematopoietic stem cells in over 90% of patients
- **Serious, chronic disease associated with increased thrombotic and cardiovascular risks[1-3]**
- **Rare disease with ~150,000 in the US and ~3.5m worldwide [4]**
  - Diagnosed typically in individuals 50-70 years of age
  - Median survival ~20 years

Treatment goal is to control HCT <45% to reduce CV and major thrombotic events

1. NORD Rare Disease Database, Polycythemia Vera. https://rarediseases.org/rare-diseases/polycythemia-vera/ 2. Spivak JL. Ann Hematol 2018; 19(2):1-14. 3. Marchioli R, et al. N Engl J Med 2013; 368:22-33 4.Using 44/100,000 global population: 7,800m, Kattamis, A. et al. Eur J Haematol (2020)

PV: Large Unmet Need and Proven Market Value Create Significant Upside for a Best-in-Class Therapy

Large Underserved Population [2-5]

- Many PV patients remain phlebotomy-dependent
- Persistent burden reflects inadequate control
- Broad addressable population needs better therapy

Current Options are Limited [2-5]

- Limitations in efficacy, safety and tolerability
- Chronic treatment burden and poor experience
- Jakafi generates ~$1B annually in PV despite later-line label limitations and treatment tradeoffs[1]

Compelling Product Profile

- Robust efficacy
- Favorable safety
- Infrequent dosing
- Better patient experience

A best-in-class PV therapy could unlock blockbuster potential in a large underserved market

1. According to Incyte financial disclosures and market share data 2. Verstovsek S, et al. Ann Hematol. 2023 Mar;102(3):571-581; 3. Verstovsek S, et al. Leuk Res. 2017; 56:5259.doi:10.1016/j.leukres.2017.01.032.; 4. McMullin MF, et. al. Br J Haematol. 2019 Jan; 184(2): 176-191.; 5. Mesa, R. Clin Adv Hematol Oncol (2017)

Divesiran Clinical Development Program
Polycythemia Vera

		Preclinical	Phase I	Phase II	Key Milestones
HEMATOLOGY	**Divesiran (TMPRSS6)**	Polycythemia Vera (PV)			
		SANRECO Phase 2, n= 48			• Topline 36-Wk Primary EP Results – Reported in August 2026 ✓
		SANRECO Phase 1, n= 21			• Completed
		GEMINI HV Study, n= 24			• Completed

Divesiran has orphan drug and fast track status in PV

Phase 2 SANRECO Study is a Global Trial: 9 Countries / 4 Continents

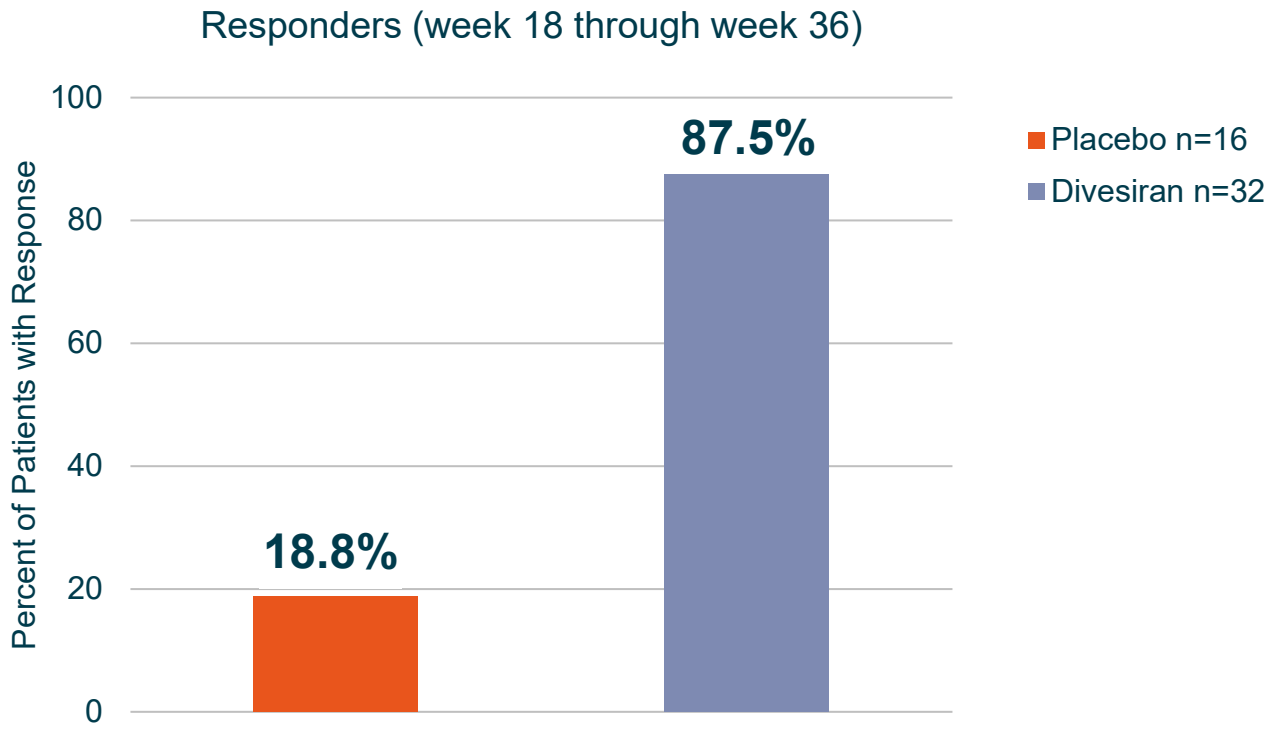
SANRECO Phase 2 Study Overview

Design	• 36-week, placebo-controlled, double-blind period followed by a 3-year, double-blind and open-label extension period evaluating divesiran in 48 phlebotomy-dependent PV patients
Key Inclusion Criteria	• PV diagnosis • At least 3 phlebotomies in the last 6 months or 5 in the last year prior to screening • Stable dose of cytoreductive agents allowed • HCT level <45% prior to dosing
Dosing & Administration	• Divesiran 6 mg vs. placebo • Administered s.c. at Q6W and Q12W intervals
Key Objectives	• Primary endpoint: proportion of patients who maintain HCT levels below 45% without phlebotomies between weeks 18 and 36 • Secondary endpoints include safety and tolerability, pharmacokinetics, and quality of life changes

SANRECO: Primary Efficacy Endpoint - Response Rate

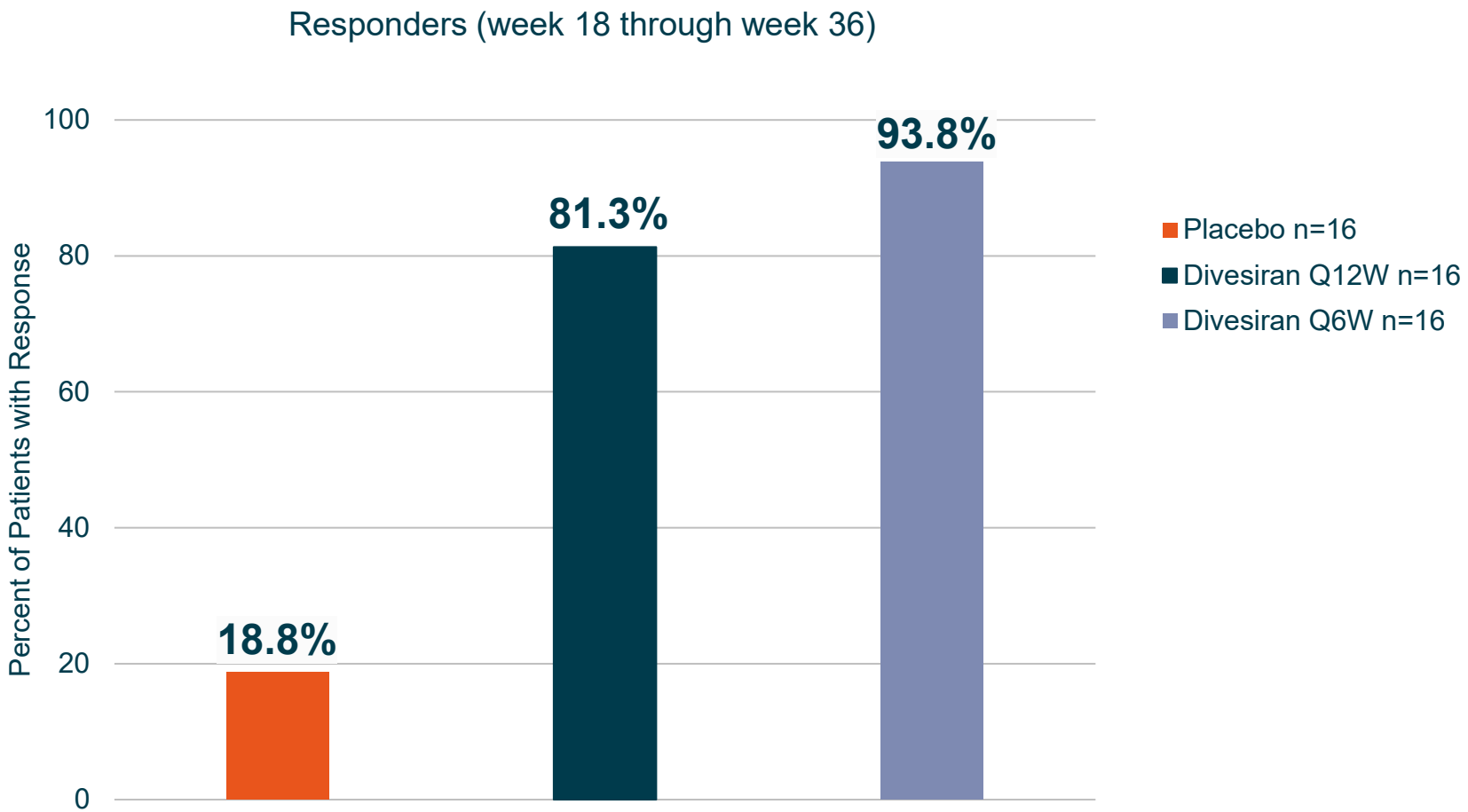
The **primary endpoint was met:**

- Significantly higher proportion of clinical responders among the divesiran treated PV patients **(88%)** compared to those who received placebo **(19%)** during weeks 18-36; p<0.0001
- **Placebo adjusted response rate = 69%**



Note: Response is defined as HCT remaining below 45% and no phlebotomies received during weeks (18-36)

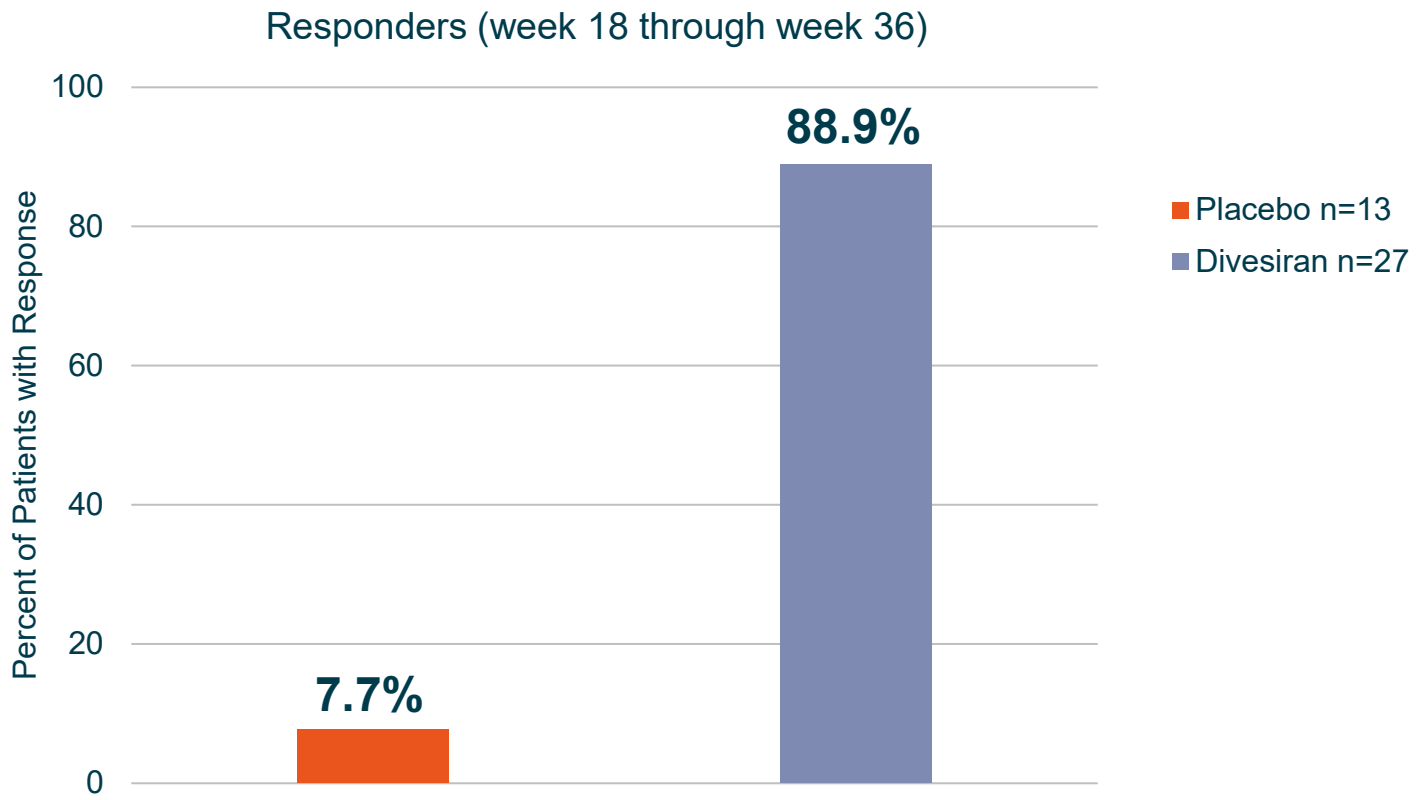
SANRECO: Primary Efficacy Endpoint by Dose Group



Note: Response is defined as HCT remaining below 45% and no phlebotomies received during weeks 18-36

SANRECO: Response Rate Sensitivity Analysis (n=40)*

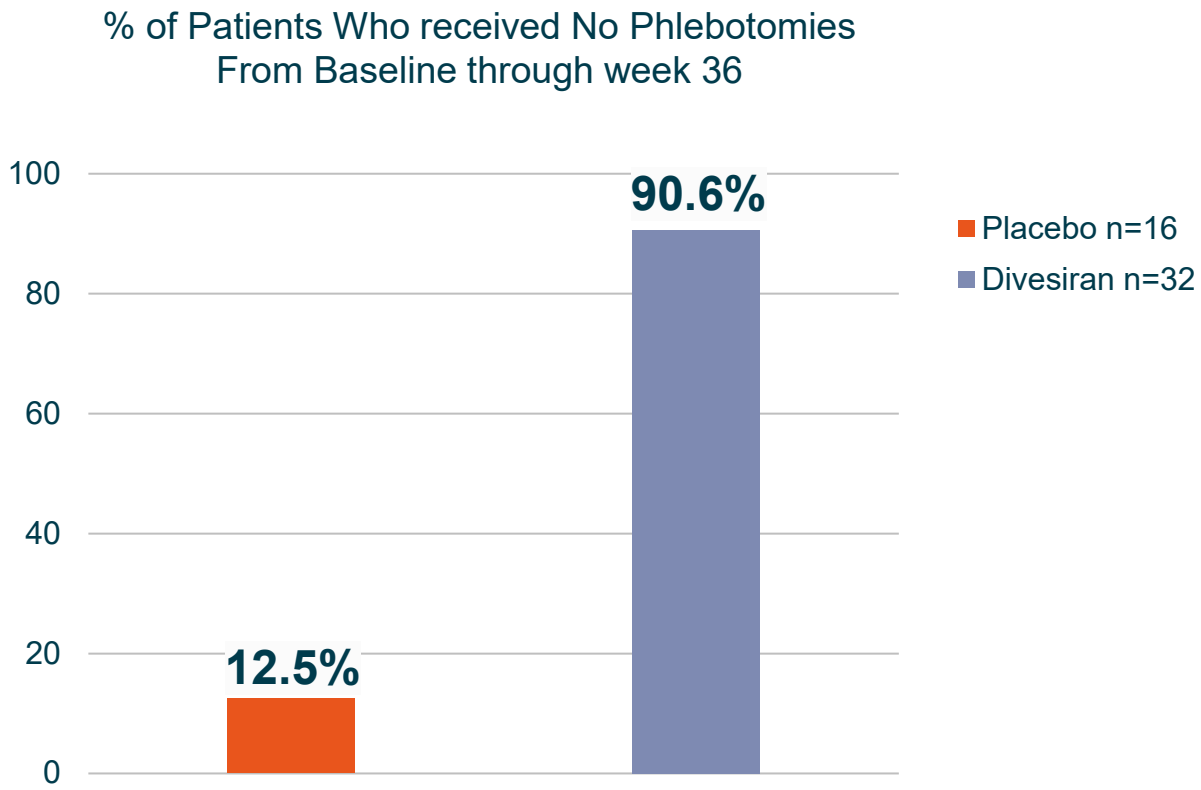
- Significantly higher proportion of clinical responders among the divesiran treated PV patients **(89%)** compared to those who received placebo **(8%)** during weeks 18-36; p<0.0001
- **Placebo adjusted response rate = 81%**



Note: Response is defined as HCT remaining below 45% and no phlebotomies received during weeks 18-36;
*All patients who met the Phase 1 criterion of a minimum of 3 phlebotomies in the previous 3 months or 5 in the previous 12 months

SANRECO: Key Secondary Endpoint - Phlebotomy Rate

- Mean number of phlebotomies in the divesiran arm was **0.2** compared to **2.1** phlebotomies in the placebo arm during weeks 0-36 ($p<0.0001$)



SANRECO: Other Secondary Endpoints

- Divesiran groups also showed improvements in:
  - Hematocrit control
  - Iron markers, including ferritin
  - Patient reported outcomes using MPN-SAF Total Symptom Score (MPN-SAF TSS)

Summary of Adverse Events (Weeks 0-36)

- Divesiran was generally well tolerated
- Safety profile was in line with previous divesiran trials; no new safety findings
- Injection site reactions were infrequent and self-limiting
- There were two investigator reported grade 1 anemia adverse event cases

SANRECO Results Support Potential Best-in-Class Treatment for Phlebotomy-Dependent PV Patients

Efficacy Endpoints

– Primary endpoint was met at both Q6W and Q12W intervals

Safety Endpoints

– Well tolerated with no new safety findings

Infrequent Dosing

– Comparable efficacy and safety results across Q6W and Q12W intervals

Phase 2 profile supports potential best-in-class positioning in phlebotomy-dependent PV

Next Steps

- Phase 2 SANRECO full results
  – Submitted abstract to ASH Congress (Dec 12-15, New Orleans)
- End of Phase 2 meeting by year end
- Initiate Phase 3 study in 1H 2027

Cardiometabolic Disease

SLN312 (ANGPTL3)

SLN312 Phase 1 Results Demonstrate a Competitive Profile for Dyslipidemia

SLN312 is a Phase 1 siRNA Silencing ANGPTL3

- ANGPTL3 inhibitors are **novel class** of therapeutic agents with **LDL receptor-independent** mechanism of action that may benefit patients that do not respond to **statins or PCSK9 inhibitors**
- Discovered as part of an ongoing **collaboration with AstraZeneca** to discover, develop and commercialize siRNA therapeutics for cardiovascular, renal, metabolic and respiratory diseases using **Silence's mRNAi GOLD™**
- **AZ completed an interim analysis of a Phase 1** trial in patients with dyslipidemia demonstrating a competitive profile; Silence will re-gain exclusive rights globally to SLN312 at the end of Phase 1

Phase 1 Data Demonstrate Competitive Profile in Patients with Dyslipidemia

- **Safe and well-tolerated** with no serious adverse events
- Robust reductions in ANGPTL3 protein after single and multiple doses of SLN312 supporting **infrequent dosing**
- **Lipid reductions** on par with other ANGPTL3i in development

Program Outlook

- Potential for **GPR146 and ANGPTL3 combination therapy** (differentiated approach)
- Several therapeutic options available including **mixed dyslipidemia, HoFH** and **HeFH**

SLN312 Phase 1 Results Demonstrate Robust ANGPTL3 Reductions Supporting Potential for Infrequent Dosing

EFFICACY	Substantial and dose-dependent reductions in ANGPTL3, triglycerides and atherogenic lipoproteins
SAFETY	Well tolerated with no major safety issues
DURABILITY	Sustained effects after single and multiple doses supporting potential for infrequent dosing

Phase 1 results presented during late breaker session at the European Atherosclerosis Society (EAS) Congress in May 2026

Cardiometabolic Disease

SLN365 (GPR146)

SLN365: Potential First-in-Class siRNA with Novel MoA in Areas of High Unmet Need

Potential First-in-Class siRNA Silencing GPR146

- Novel mechanism-of-action for managing cholesterol levels independent of LDL receptor (LDLR) function
- Hypercholesterolemia is a highly prevalent indication: around 1 in 300 individuals worldwide have the familial form HeFH (heterozygous) and around 1 in 300,000 worldwide have HoFH (homozygous) [1,2]

Demonstrated Preclinical Proof-of-Concept

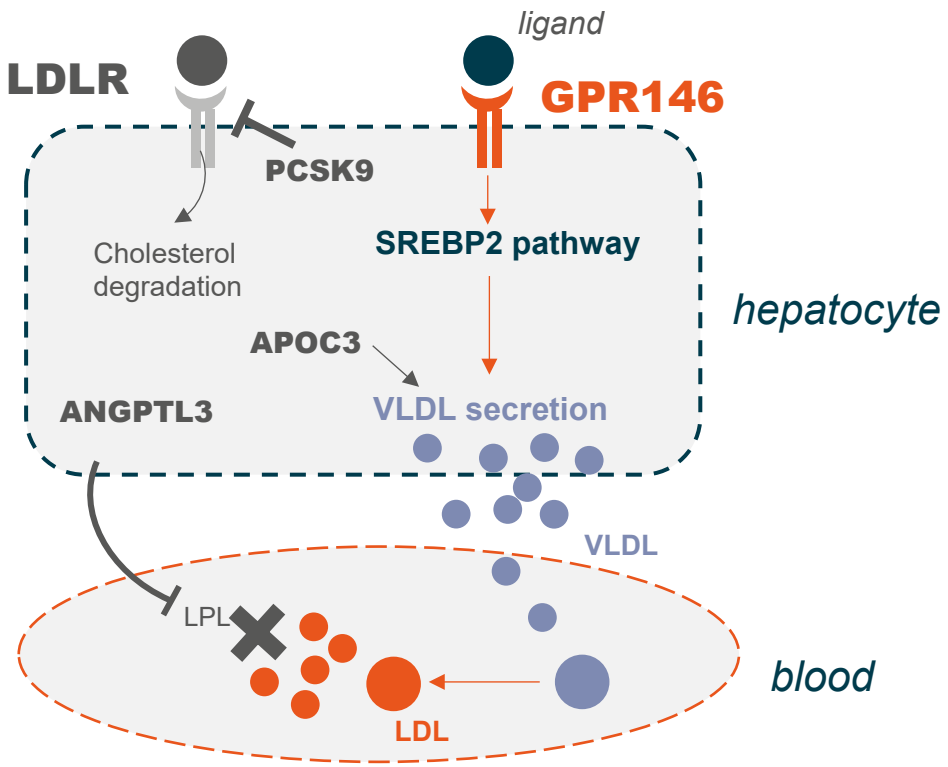
- Achieved >80% mRNA knockdown after a single injection (non-human primates)
- Sustained effects throughout study with ~50% or greater mRNA knockdown observed 3 months after dosing (NHP)
- Significant reductions in total cholesterol, LDL-C and triglycerides in murine disease model (LDLR KO)

Program Outlook

- Potential IND filing in 2H 2027
- First potential indication planned for the treatment of HoFH which is the area of highest unmet need where >90% of patients don’t reach the LDL-C goal despite being treated with multiple lipid lowering therapies

1. Heterozygous familial hypercholesterolemia: prevalence and control rates I 2021; 2. Homozygous Familial Hypercholesterolaemia – Worldwide Experience I 2023

GPR146: Novel Target for the Management of Cholesterol Independent of LDL Receptor Function



LPL=Lipoprotein Lipase
Note: Cholesterol modulating mechanism in other tissues not represented

- GPR146 is a receptor present on hepatocytes and plays an **important role in VLDL regulation**
- Inhibition of GPR146 **reduces release of VLDL & circulating levels of TG and LDL-C**
- GPR146's function is **independent of LDLR**
- **Potential for synergistic** use with LDLR-dependent drugs
- **Potential to Reduce** Dependency on **Lipoprotein Apheresis**

Angiopoietin-Like Protein 3 (ANGPTL3) Modulates Lipoprotein Metabolism and Dyslipidaemia

Genetic Evidence: GPR146 Deficiency Protects Against Hypercholesterolemia and Atherosclerosis

TRANSLATIONAL SCIENCES

Variants in the *GPR146* Gene Are Associated With a Favorable Cardiometabolic Risk Profile

https://doi.org/10.1161/ATVBAHA.122.317514

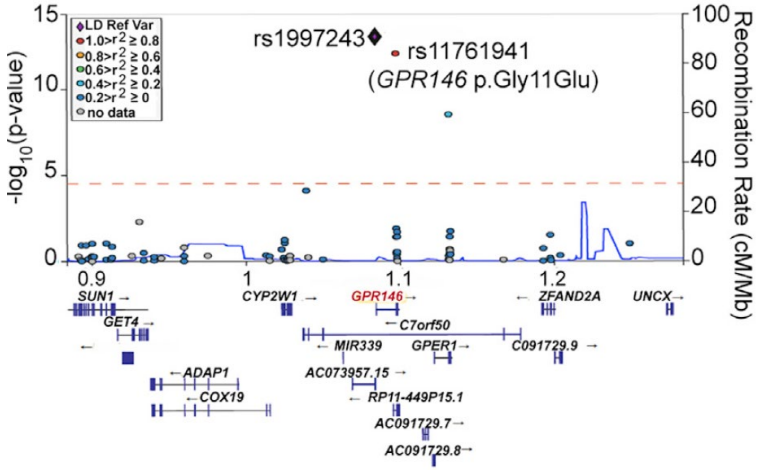
Cell Research

Hypercholesterolemia risk associated GPR146 is an orphan G-protein coupled receptor that regulates blood cholesterol level in human and mouse

https://doi.org/10.1038/s41422-020-0303-z

Cell

GPR146 Deficiency Protects against Hypercholesterolemia and Atherosclerosis

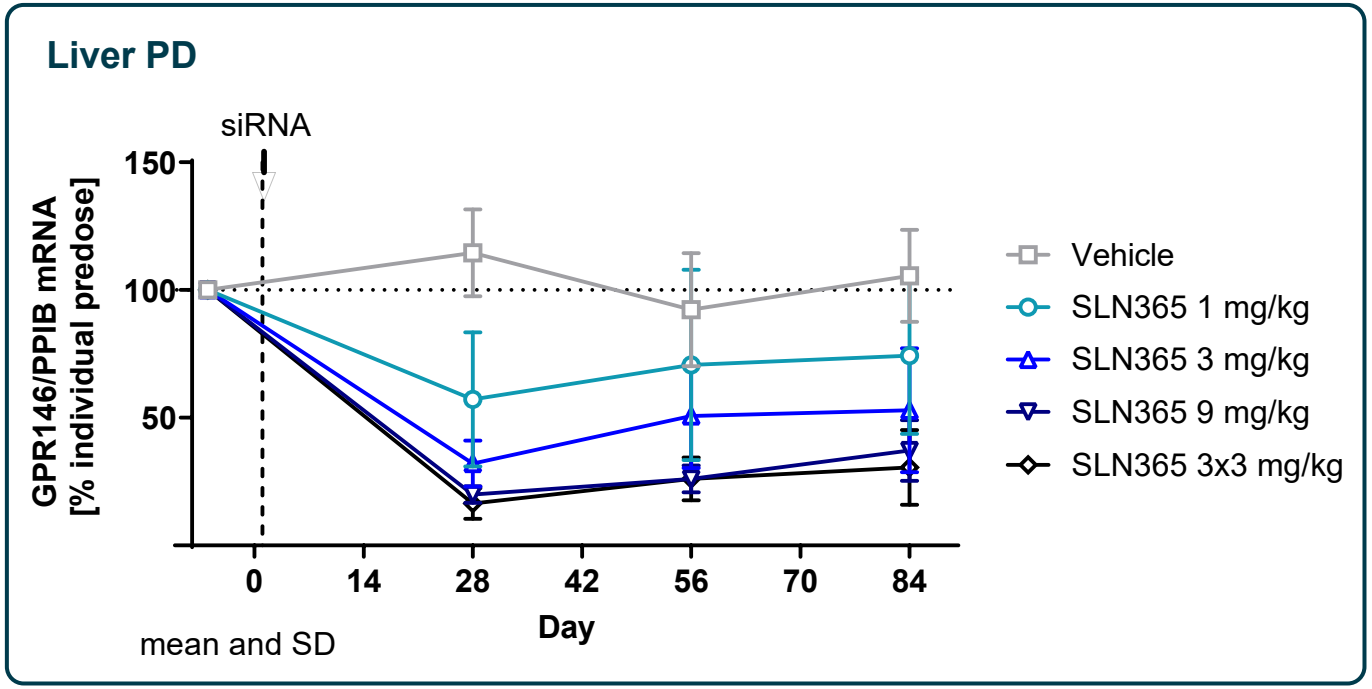


https://doi.org/10.1016/j.cell.2019.10.034

Human Genetic Studies Support GPR146 as a Susceptible Gene Regulating Cholesterol Levels

Common rs2362529-C allele → lower GPR146 expression → lower LDL-C, ApoB, HDL, apoAI, and CRP
Common rs1997243-G allele → higher GPR146 expression → exact opposite phenotype

SLN365 Demonstrated Dose-Dependent GPR146 mRNA Knockdown in Non-Human Primates

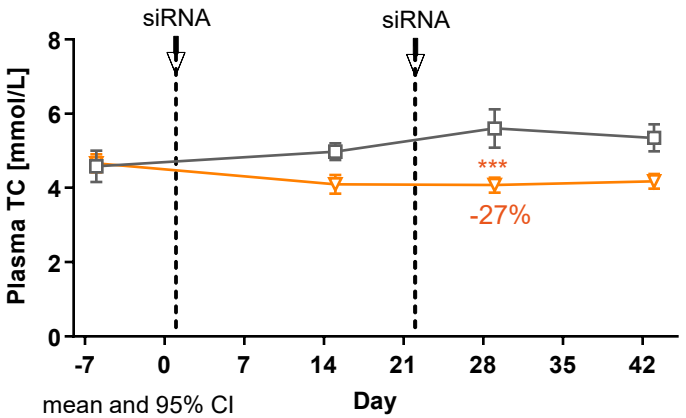


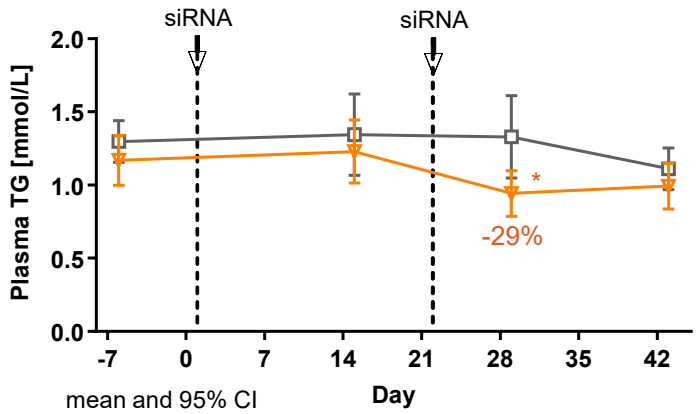
Results

- SLN365 treatment resulted in 84% mRNA KD at 4 weeks in the multiple dose group (3 x 3 mg/kg)
- Sustained KD throughout the study duration – 70% mRNA KD at week 12 in the multiple dose group
- Single dose of 9 mg/kg resulted in 80% mRNA KD at 4 weeks and 63% KD at week 12
- No major treatment-related effect on body weight and no effect on clinical chemistry, hematology or clinical observation

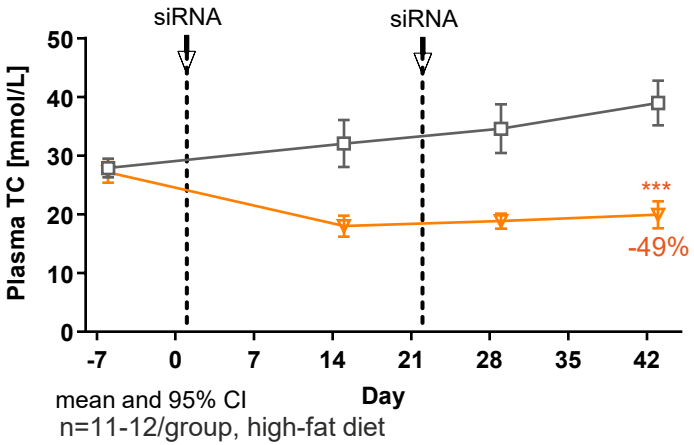
Reduction of Plasma Cholesterol and Triglycerides in Mice Following GPR146 siRNA Treatment

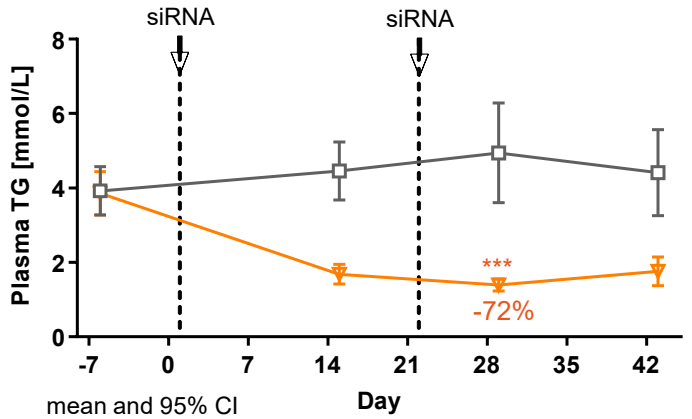
WT





LDLR KO





- Mouse surrogate siRNA reduced GPR146 *mRNA* levels by >75%
- Significant reduction of total cholesterol and triglycerides following siRNA treatment observed in WT and LDLR KO mice on Western diet
- No accumulation of lipids in the liver following siRNA treatment

PBS Gpr146 siRNA

Dunnet's test on two-factor linear model with interaction
*** P < 0.001; * P<0.05 compared to PBS control
Data shown for one compound, similar data was obtained with two different siRNAs

Cardiometabolic Disease

SLN098 (INHBE)

SLN098 Targets INHBE: Promising Novel Target for Cardiometabolic Disease

Potential to Address Multiple Unmet Needs in Cardiometabolic Disease

- SLN098 has potential to address unmet needs including reducing total and visceral fat, improving muscle preservation, and slowing weight regain
- INHBE is a novel target supported by human genetics, strong preclinical data, and fast emerging clinical data demonstrating early efficacy and safety in humans

Demonstrated Deep and Durable Knockdown in NHP

- ~ 90% knockdown of INHBE protein levels sustained for at least 3 months in NHPs
- Obesity mouse model data validated MoA including significant **reduction in visceral fat** and **preservation of lean mass**

Program Outlook

- Potential IND filing by 2027 year-end
- Multiple development opportunities either as monotherapy or through strategic combinations

Despite Recent Advances in Obesity Treatment, Limitations of Current SoC Leave Millions at Risk of Further Complications

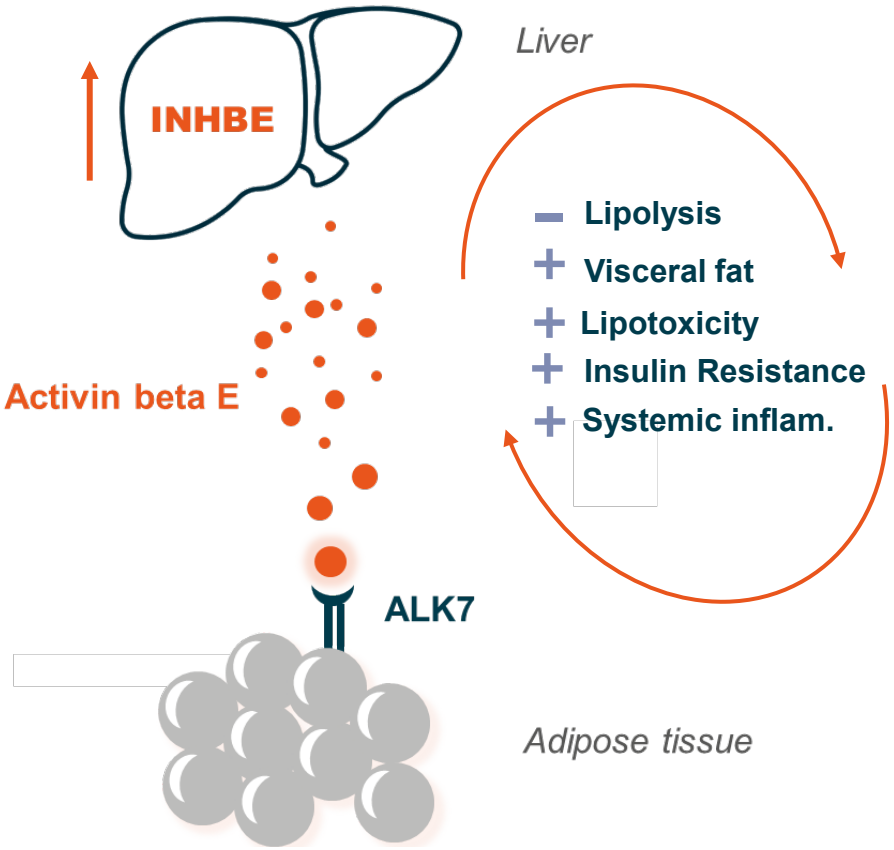
- ~ 1 billion patients worldwide affected by obesity and associated comorbidities
- Current obesity treatments offer weight loss of ~15-25% which plateaus after 12-24 months and are associated with up to 40% lean muscle mass loss
- More than two-thirds weight loss is regained within first year after discontinuation of treatment
- Poor tolerability and compliance with up to 30% patients discontinuing GLP/GIP agonists treatment

Need for Improved Quality of Weight Loss with Differentiated Approach to Current Treatments

1. NCD-RisC, Lancet. 2024; 2. Melson et al Clinical Research 2024; 3. Kevin Hall, bioRxiv. 2023; Wilding et al, NEJM. 2021; Jastreboff et al, NEJM.2022; 4.Gomar et al, Curr Cardiol Rep. 2025; 5. West et al, BMJ.2026

Targeting INHBE Expression Blocks Signalling via ALK7, Effectively Enabling Lipolysis in Adipose Tissue

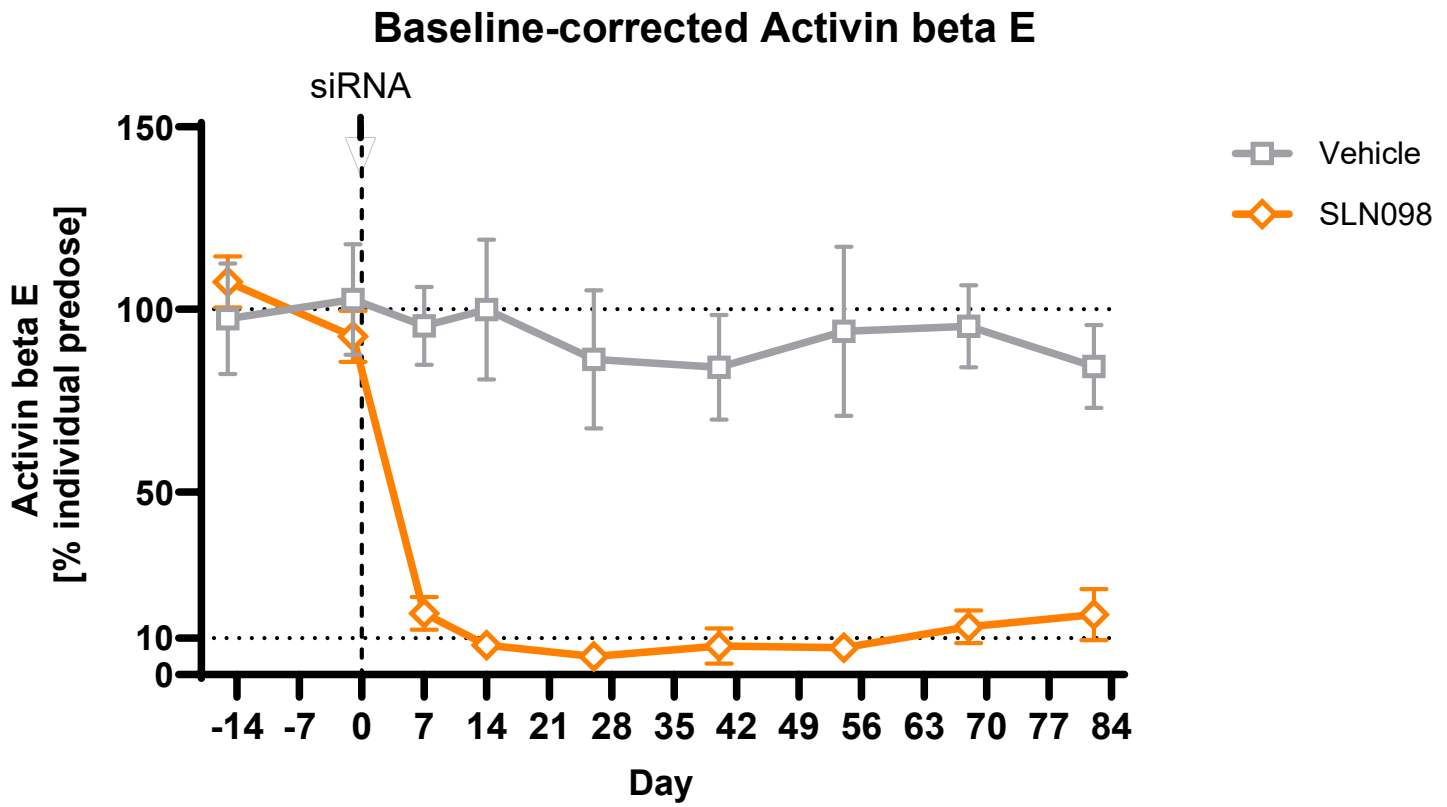
Pathogenic state



Deaton et al Nature Comm. 2022, Sugiyama et al 2018; Akbari et al 2022

- ☑ INHBE (Inhibin beta E) encodes **Activin beta E**
- ☑ **Expression is elevated** upon fasting in **obesity** and in patients with **T2D**
- ☑ Activin beta E **activates ALK7** in adipocytes, where it **blocks lipolysis & promotes fat storage**
- ☑ **Inhibition of INHBE** expression **enhances lipolysis** and **redistributes fat**

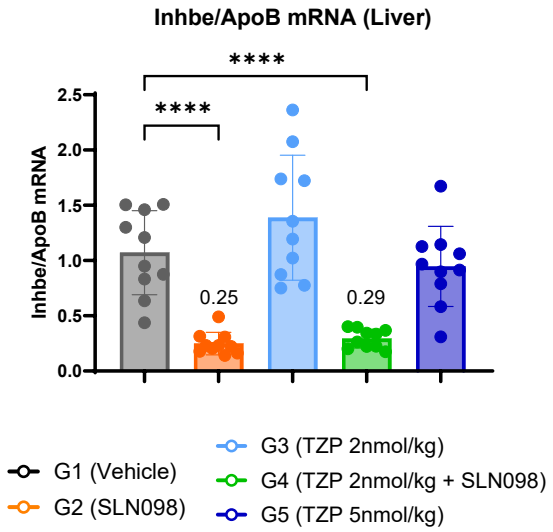
SLN098 Demonstrated Deep and Durable Knockdown in NHP: ~90% Protein Knockdown Sustained for at Least 3 Months

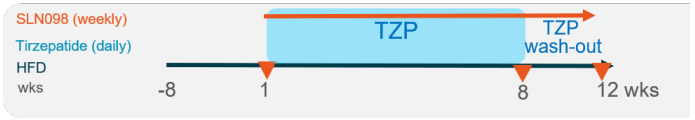


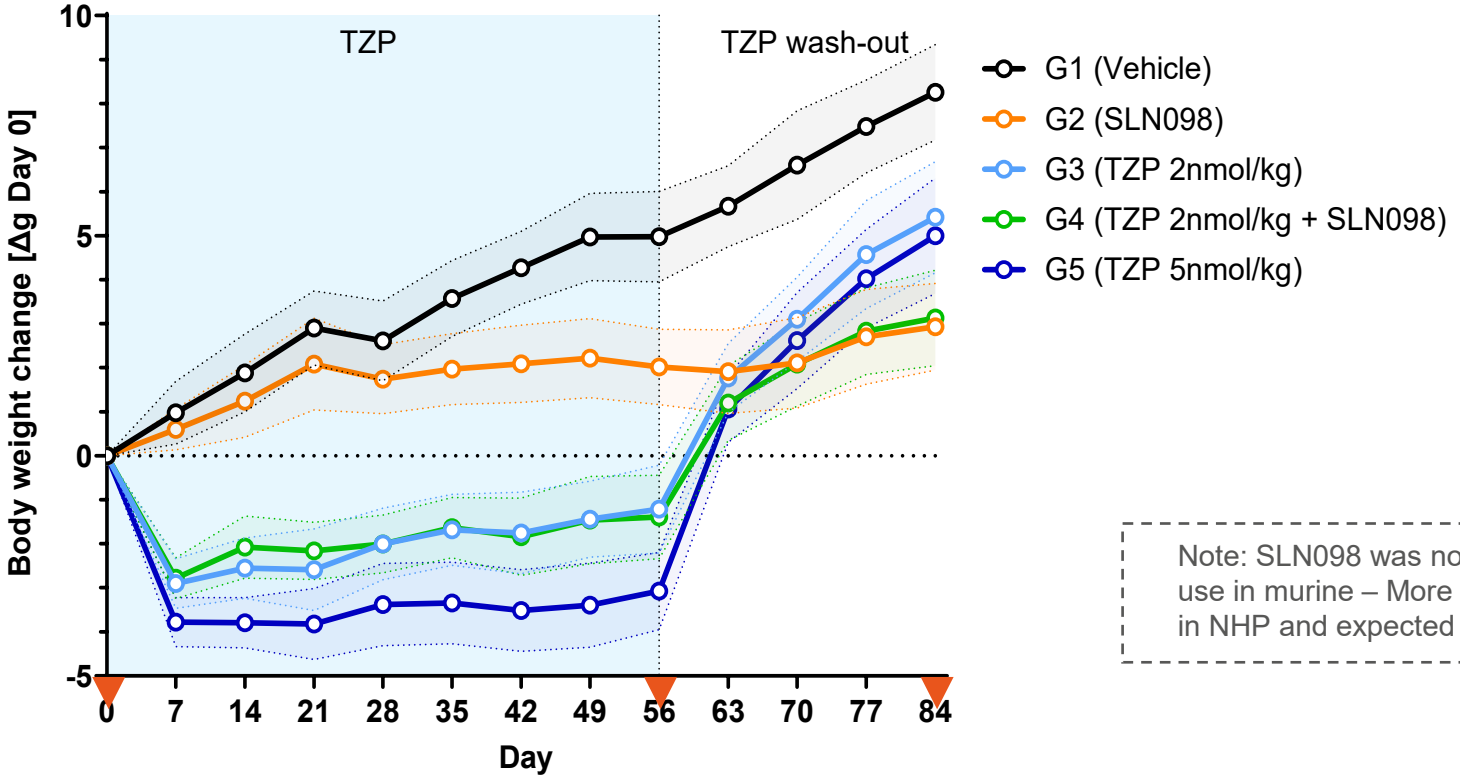
mean and SD, n=3

SLN098 Significantly Reduces Weight Gain in Mice on High Fat Diet Both as Monotherapy and Post Tirzepatide Discontinuation

Murine Obesity Mouse Model – Mono Therapy vs Co-treatment with Tirzepatide (TZP)





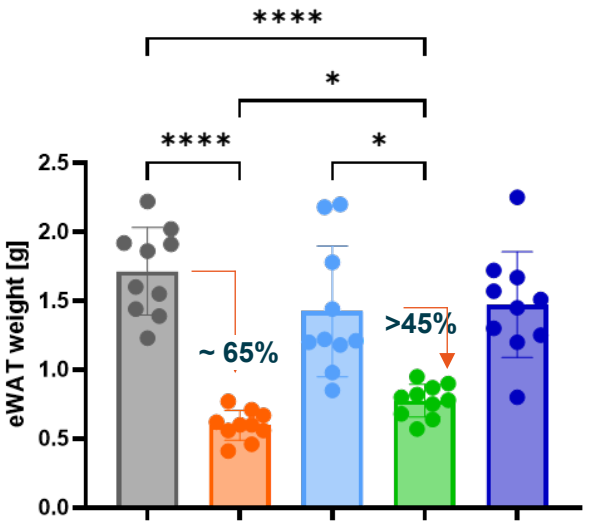


Mean and 95%CI

Note: SLN098 was not optimized for use in murine – More robust KD seen in NHP and expected in humans

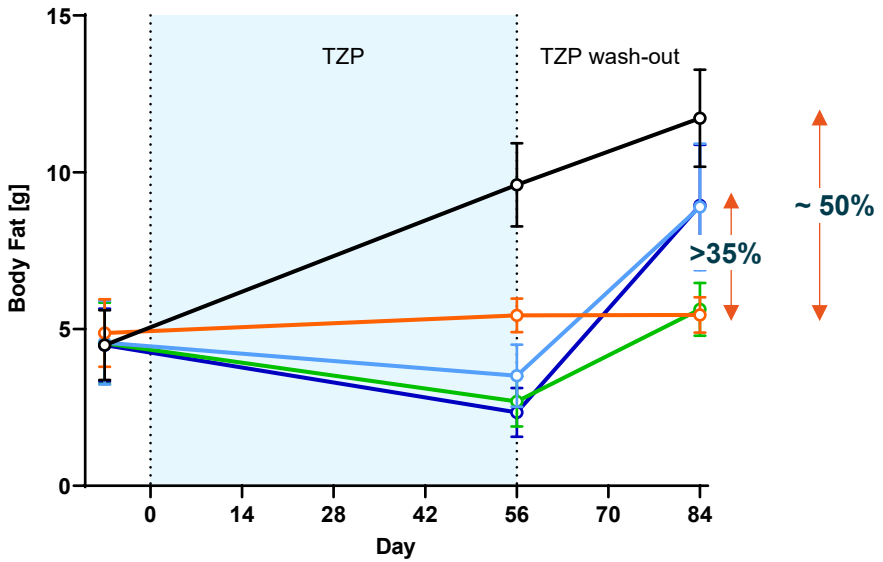
SLN098 Monotherapy Lowers Visceral Fat and Total Fat Gain While Preventing Lean Mass Loss in Combination with TZP

eWAT Weight [D84]



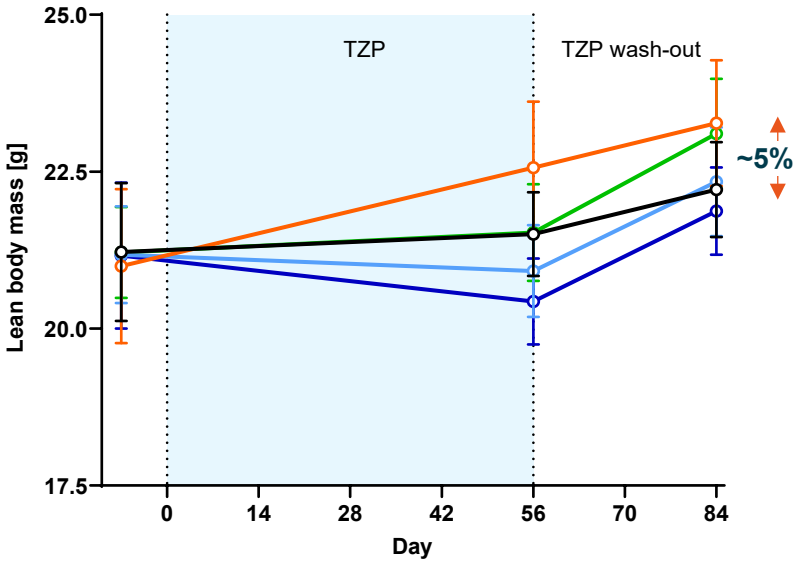
Read out at week 12
TZP was discontinued at week 8

Body Fat [g]



Mean and 95%CI

Lean Mass [g]



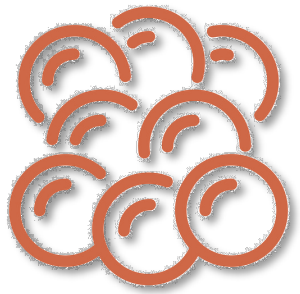
Mean and 95%CI

G1 (Vehicle)
G2 (SLN098)
G3 (TZP 2nmol/kg)
G4 (TZP 2nmol/kg + SLN098)
G5 (TZP 5nmol/kg)

Potential to Address Major Unmet Needs Through Strategic Combinations

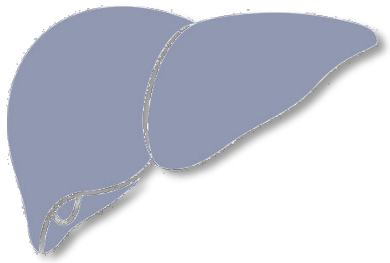
Improve Quality of Weight Loss

+ Incretins



Tap into Atherogenic Dyslipidaemia and Associated Metabolic Disorders

+ Lipid Modifiers



Skeletal Mass Preservation

+ Lean Mass Sparing Therapies

Achieved and Anticipated 2026 Milestones

	1Q 2026	2Q 2026	3Q 2026	4Q 2026
Divesiran Polycythemia Vera			✓ Ph2 topline data	EOP2 FDA Meeting ★ Ph2 data presentation
Zerlasiran High Lp(a)		*Results from first industry CVOT in high Lp(a) anticipated in 2026*		
SLN312* Dyslipidemia		✓ Ph1 late-breaker at EAS Congress		
SLN365 HoFH		✓ Preclinical data IND enabling studies (potential filing in 2H 2027)		
SLN098 Obesity		✓ Preclinical data IND enabling studies (potential filing in 2H 2027)		
Extra-hepatic		✓ Preclinical data		★ Preclinical data

EOP2 Meeting: End-of-Phase 2 meeting with FDA planned by year end. *SLN312 is currently licensed to AstraZeneca. As announced in a Company Press Release dated March 5, 2026, Silence will re-gain exclusive rights globally to SLN312 following Phase 1. HoFH=Homozygous familial hypercholesterolemia

Silencing diseases through precision engineered medicines created with proprietary siRNA technology

SILENCE THERAPEUTICS