SILENCE THERAPEUTICS

Silence Therapeutics

Corporate Presentation

September 2020

Forward Looking Statements

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Silence Therapeutics - Summary

Valuable Platform	> Reproducible, proprietary gene silencing (RNAi) therapeutics platform, rapidly generating internal pipeline and out-licensing options. Platform validated through collaborations with AstraZeneca, Mallinckrodt and Takeda
Growing Clinical Pipeline	> SLN360 (CVD with high LP(a)) - IND approved by FDA to start Phase 1 studies > SLN124 (β-Thalassemia and MDS[1]) – initiated dosing in Phase 1 study in healthy volunteers > SLN500 (C3) - preclinical work ongoing
Strong Experienced Team	> Pioneers in siRNA for over 18 years, growing clinical team, and experienced biopharma Board and Management team > Appointed experienced biopharma CEO – Mark Rothera – to lead next phase of growth
Target Selection	> Focused on targeting indications in rare diseases and large population targets, including new medicines for cardiovascular disease and complement-mediated diseases
Strong Financial Position	> Strong financial position with a cash runway extending beyond key clinical milestones such as SLN360 and SLN124 Phase 1 trial readouts

HQ in London



R&D in Berlin



+ New office in New York

Approx. 60 employees across all sites

Notes:
[1] MDS = Myelodysplastic syndrome

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Leadership

President and CEO
Mark Rothera

- Appointed as President and CEO in September 2020
- Over 30 years of experience in the biopharmaceutical industry including driving the transition of multiple emerging biotech companies from R&D stage to commercialization
- Former President & CEO of Orchard Therapeutics and CCO of PTC Therapeutics



Head R&D, CMO
Giles Campion

- Former Chief Medical Officer and SVP R&D at Prosensa (2009-2016), playing a major role in their Nasdaq IPO and subsequent sale to Biomarin for $680m
- Most recently CMO at Albumedix
- Spent 4 years in senior R&D roles at Novartis
- Medical degree and doctorate from Bristol University



CFO
Rob Quinn

- Chartered accountancy training at Deloitte before joining GSK
- Area Finance Director for Africa and Developing Countries at GSK
- Joined Silence in early 2017 as Head FP&A
- PhD in Biochemistry from the University of Manchester



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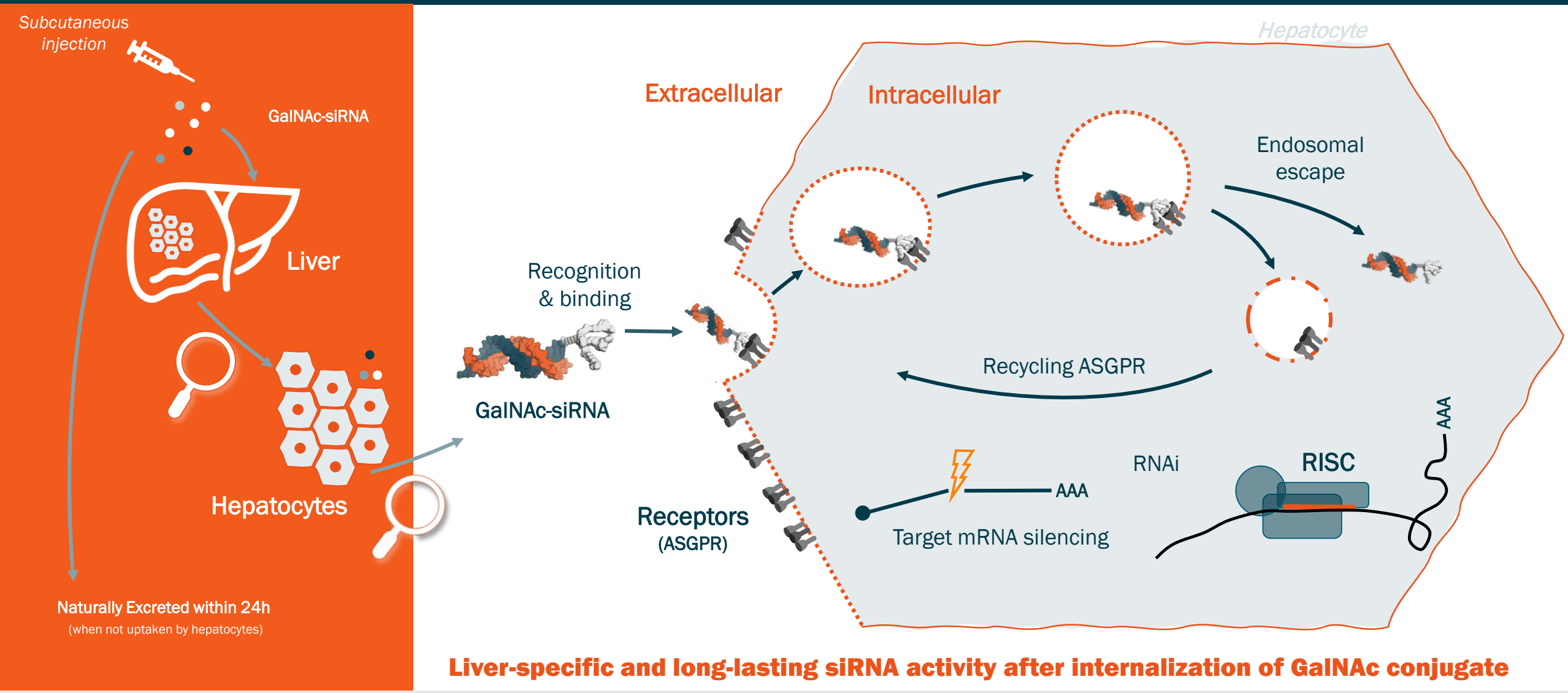
GalNAc (Ligand) Conjugation Allows for Delivery of siRNA to Liver Cells



Liver-specific and long-lasting siRNA activity after internalization of GalNAc conjugate

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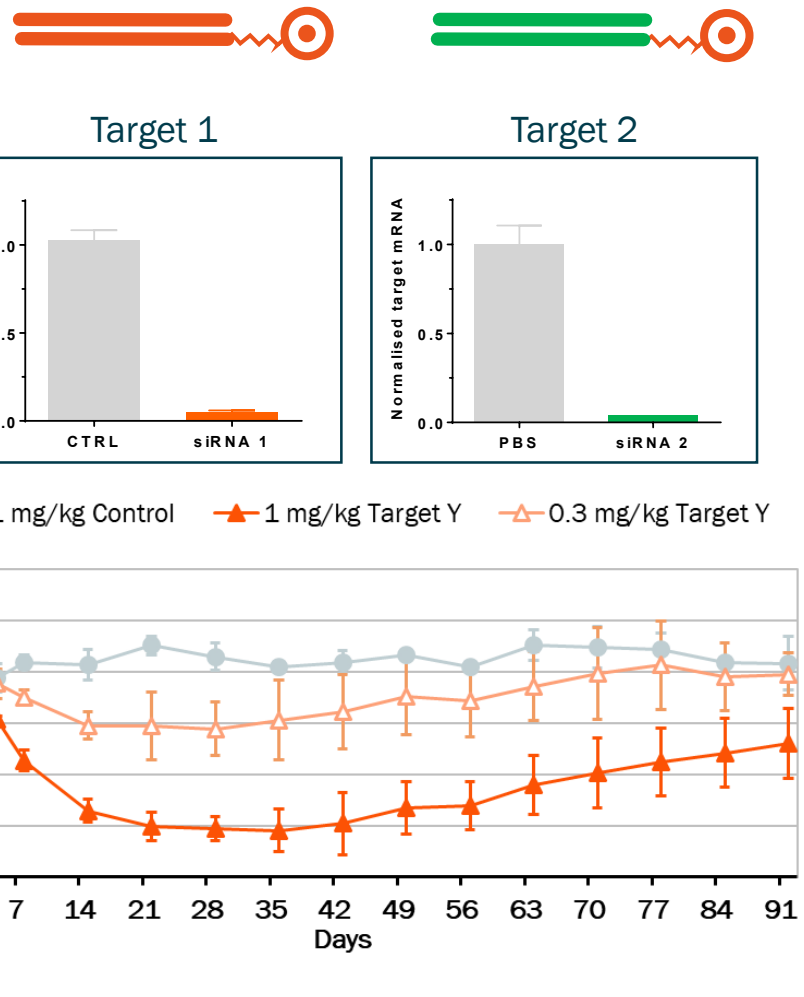
Reproducibly Silencing Disease-Associated Genes Using our Proprietary Platform Technology

Platform delivery technology: GalNAc-siRNA able to mediate highly specific gene silencing in hepatocytes (liver) – "Specificity upon specificity".

Patient friendly: Subcutaneous delivery and infrequent dosing (monthly or longer). Well tolerated[1].

~7,000 proteins expressed in the liver. Silence can target any of them by adapting the siRNA sequence, using the same technology.

[1] Well tolerated in animal models tested.



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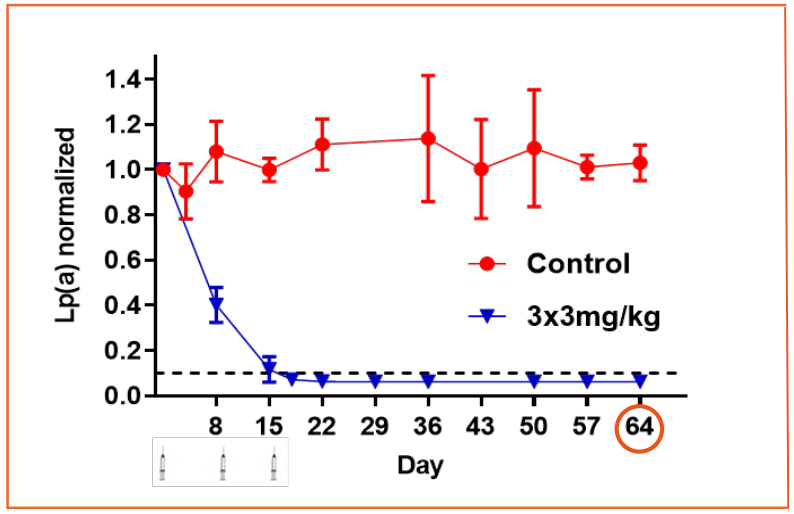
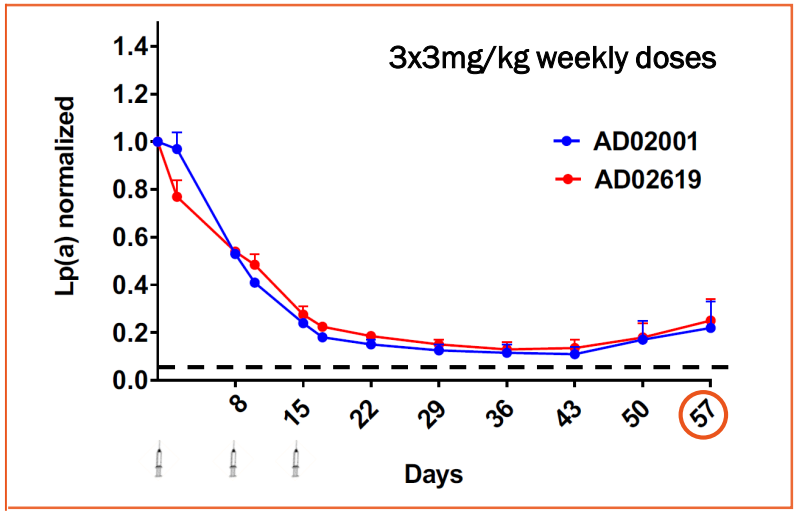
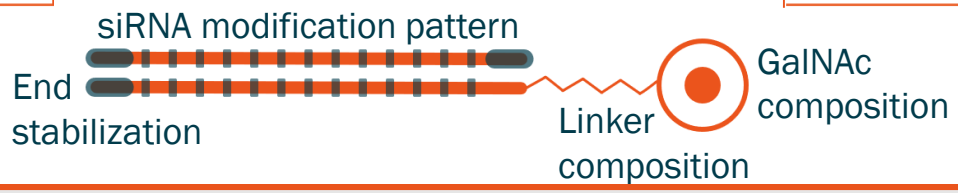
A Competitive Platform, With Continuous Fine-Tuning to Further Improve Performance

SLN360



AMG 890





- **Modification pattern:** number of non-natural modifications reduced from c.50% to <15% through the discovery of novel modification patterns
- **End stabilization:** increased circulation half-life, increased activity and duration of action
- **Linker:** simplified and flexible synthesis, increased activity, and option to control circulation and intracellular half-life
- **GalNAc:** 2-3 fold increase in activity achieved through optimization of number and placement of GalNAc units
- **IP:** 10 siRNA chemistry patent applications filed 2017-2019

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

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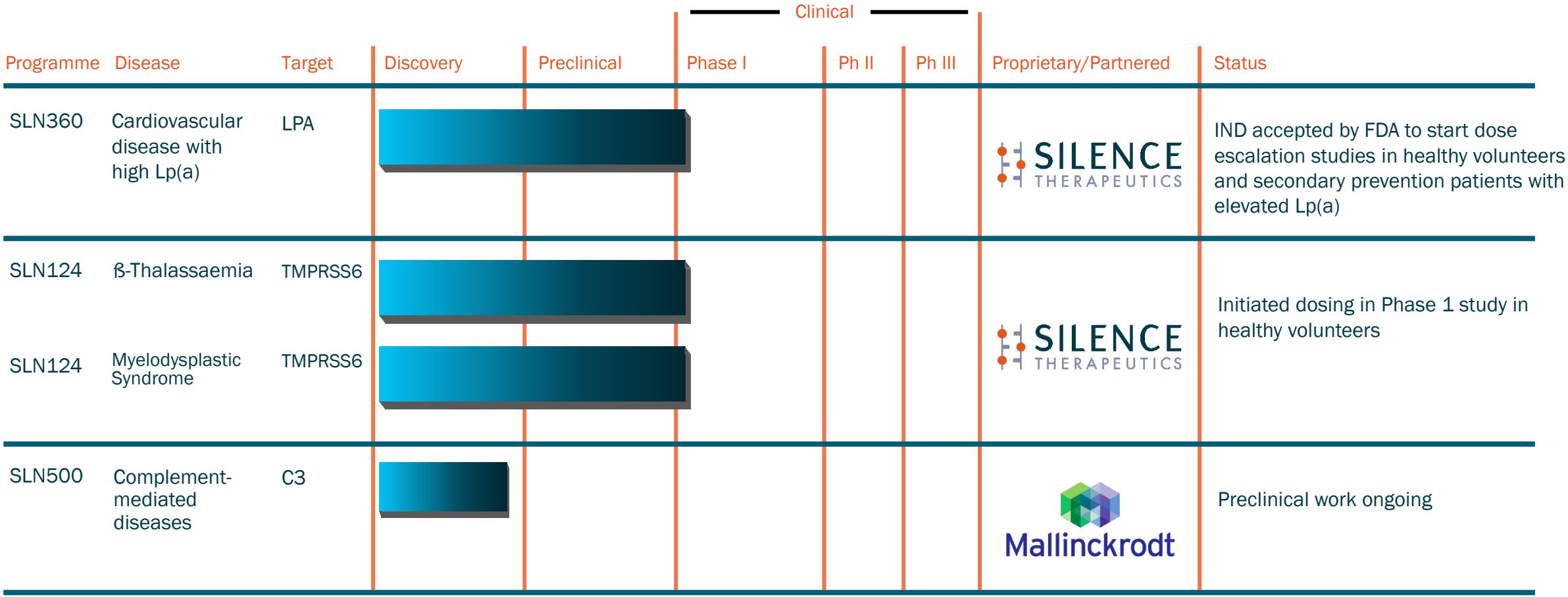
Development Pipeline



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High-Value Collaborations – Expanding Pipeline Opportunities

AstraZeneca

- Signed major deal to discover, develop and commercialise siRNA therapeutics for cardiovascular, renal, metabolic and respiratory diseases in March 2020
  - Upfront cash payment of $60 million and an equity investment of $20 million[1]
  - Up to $400 million in potential milestones for each target plus tiered royalties

Takeda

- Commenced technology evaluation to explore the potential of using our platform to generate siRNA molecules against a novel, undisclosed target in January 2020

Mallinckrodt

- Expanded complement pathway RNAi collaboration in July 2020
  - > Mallinckrodt exercised option to license two additional complement targets
  - > Initiated work on second target and triggered $2M milestone payment

[1] Of the $60m, $20m was paid in May 2020 and a further $40m is unconditionally payable in H1 2021.

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SLN360
for the treatment of

Cardiovascular Disease with high Lp(a)



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Lp(a): What is it?

Discovered in 1963 by Kare Berg

Expressed predominantly in the liver

> Highly variable in size

> Expression restricted to human and non-human primates

Lp(a) levels are genetically defined

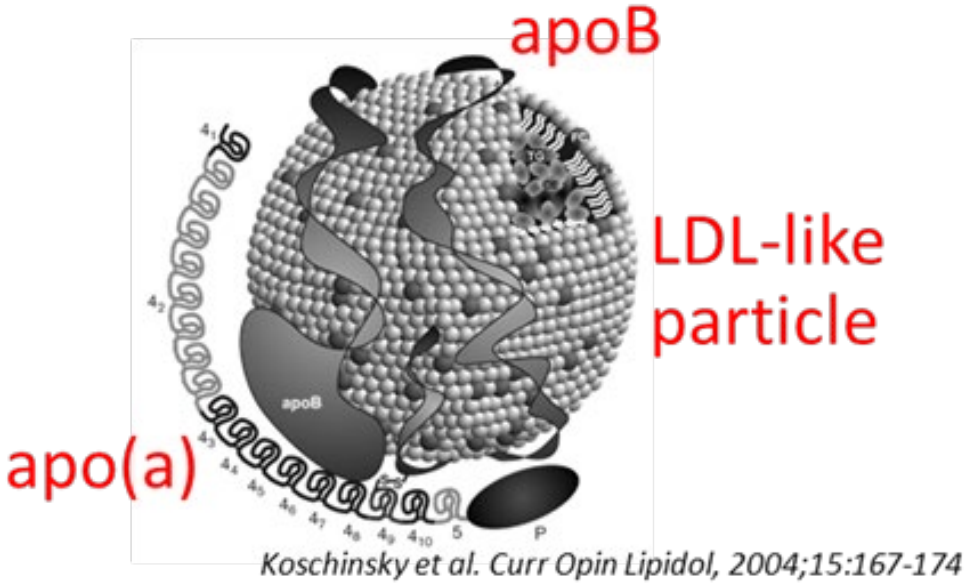
> Not modified through lifestyle interventions

Contributes to total LDL-C

Considered to be pro-atherogenic, pro-thrombotic and pro-inflammatory

Major untreated risk factor in CVD

> Currently approved therapies do not address Lp(a)



Koschinsky et al. Curr Opin Lipidol, 2004;15:167-174

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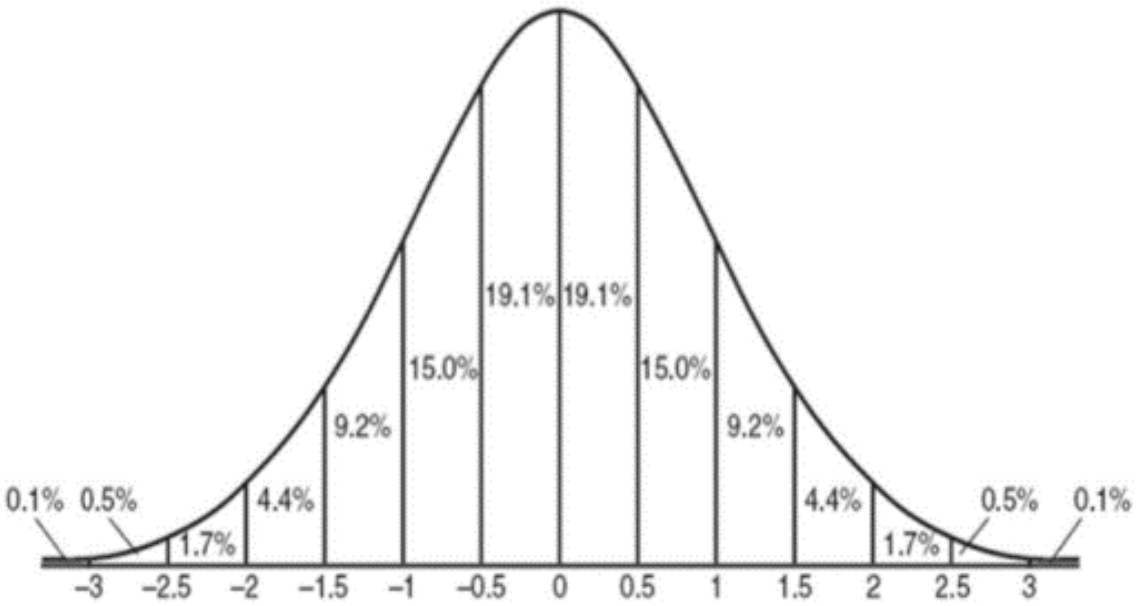
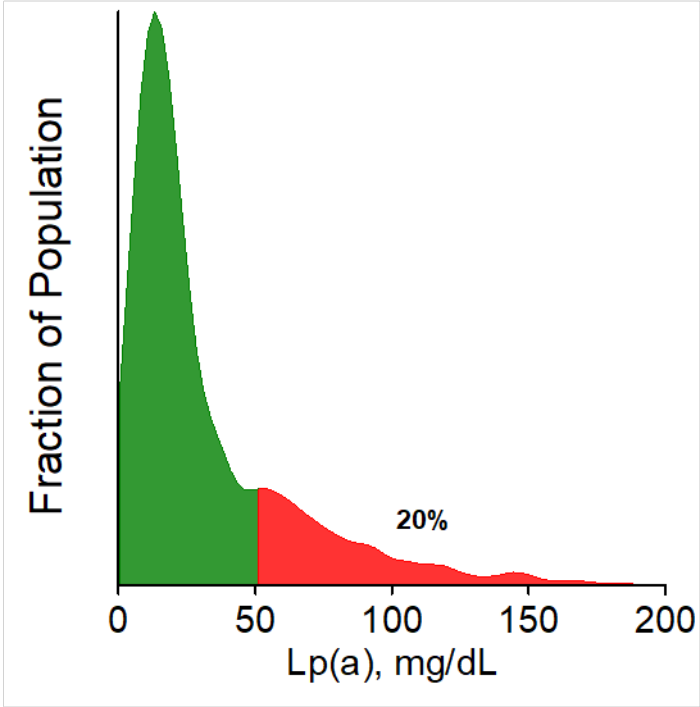
Lp(a) Distribution in the Population

Most biological entities show a normal distribution in a population



Lp(a) distribution is skewed with 20% of the population with higher than 50 mg/dL



Nordestgaard B Eur Heart J: 2010 31:2844

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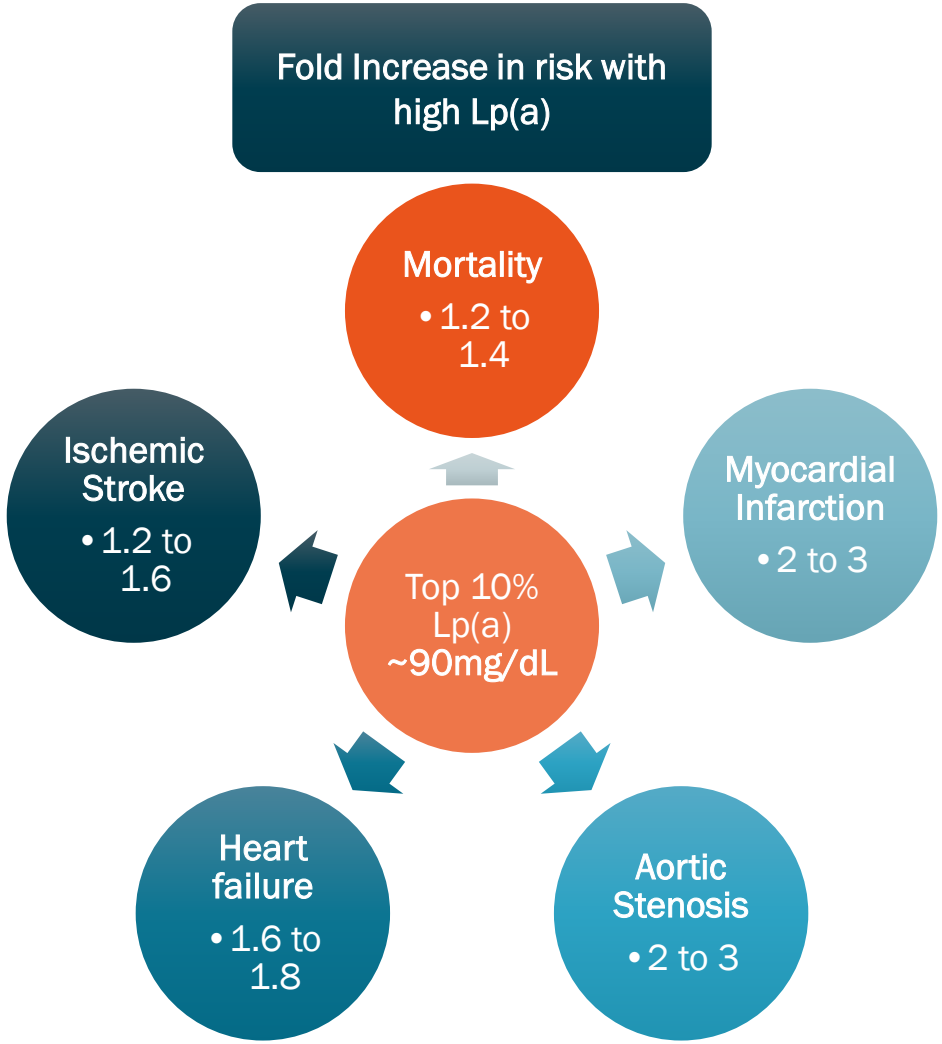
Cardiovascular event risk increases with high Lp(a)

Risk Ratio:

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



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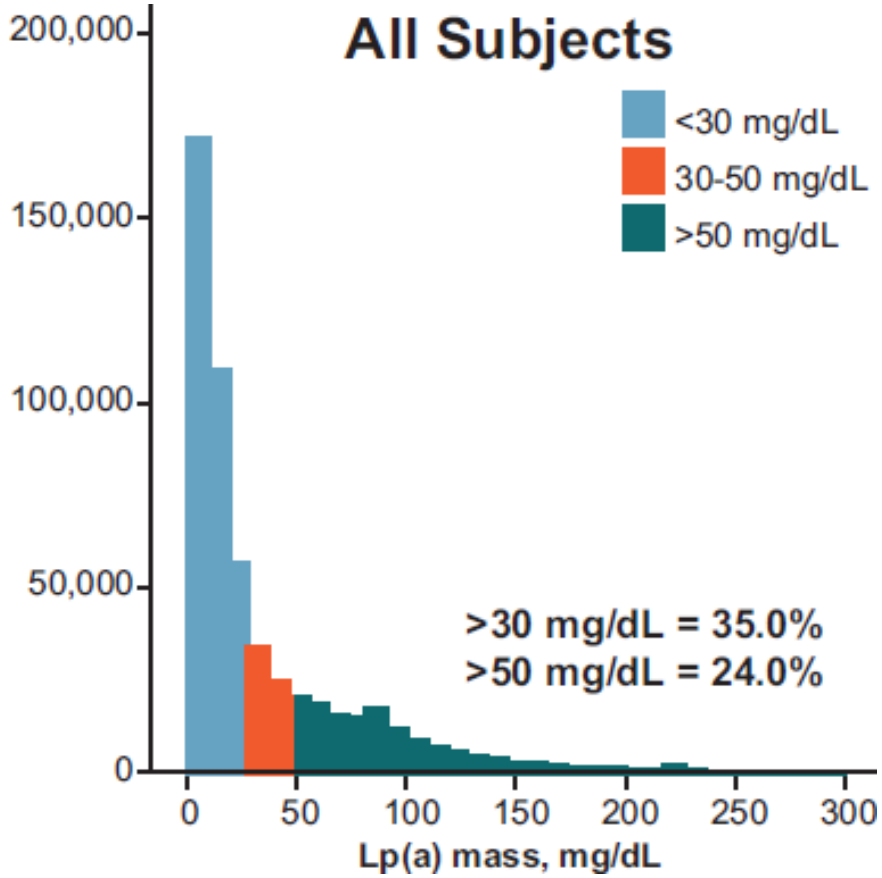
Up to 700 million globally in top 10% Lp(a) levels



Source: US laboratory Database in 531,144 patients

Global Prevalence of Elevated Lp(a) [millions]

Prevalence	20%	10%	5%	1%
Lp(a) [mg/dL]	*60*	*90*	*116*	*180*
USA	64	30	16	3.2
EU	150	75	37.5	7.5
Globally	1400	700	350	70

Varvel et al Arterioscler Thromb Vasc Biol. 2016;36:2239

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SLN360 Targets Lp(a) - an Independent Risk Factor for Cardiovascular Disease

Lp(a) levels are genetically determined

Recognized as a major untreated risk factor in cardiovascular disease

Lp(a) levels are not significantly modifiable through diet or approved pharmacological therapies

Large population worldwide with up to 10% with >90mg/dL (2x increased MI risk)

Multiple mechanisms by which Lp(a) causes CVD

> Pro-atherogenic
> Pro-thrombotic
> Pro-inflammatory

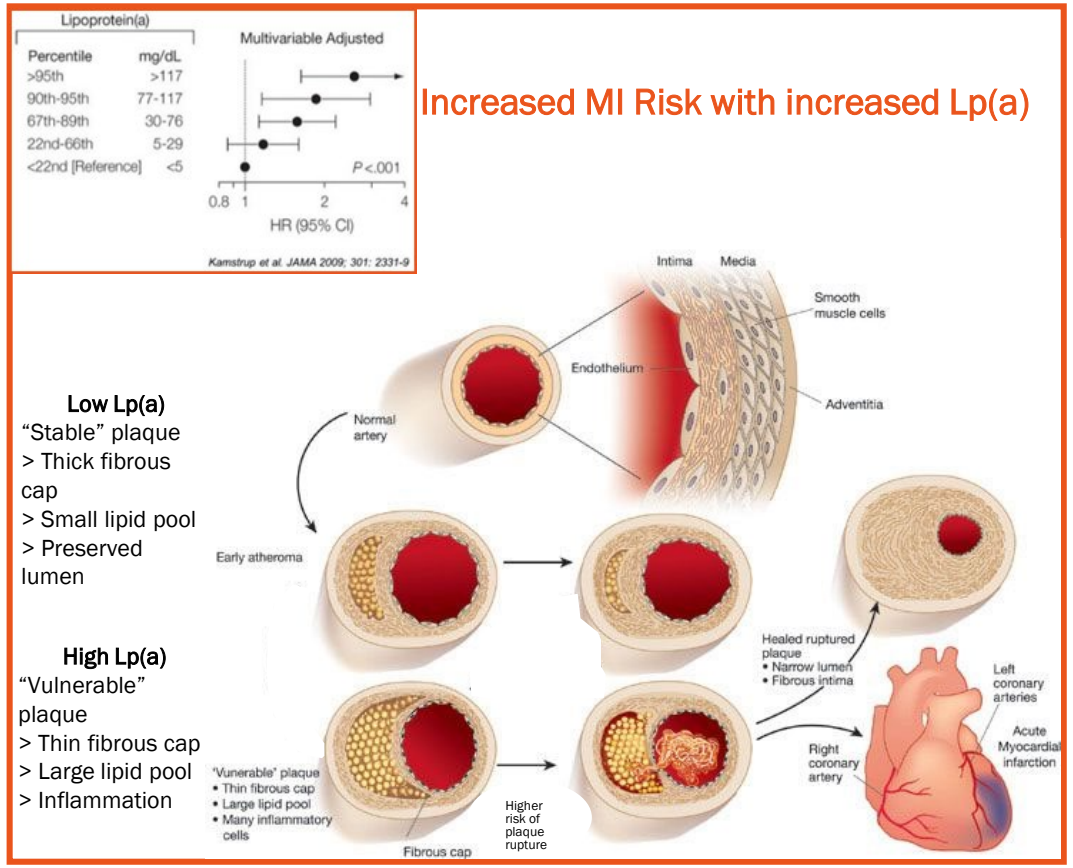

Image modified from Libby 2002, Nature 420, 868

Targeting Lp(a) with SLN360 has the potential to address major unmet needs in cardiovascular disease

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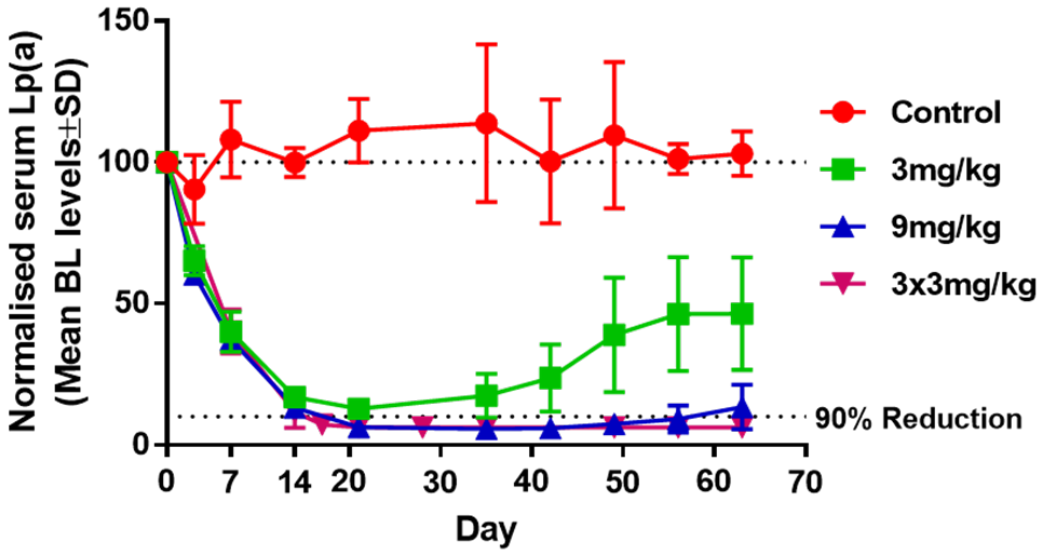
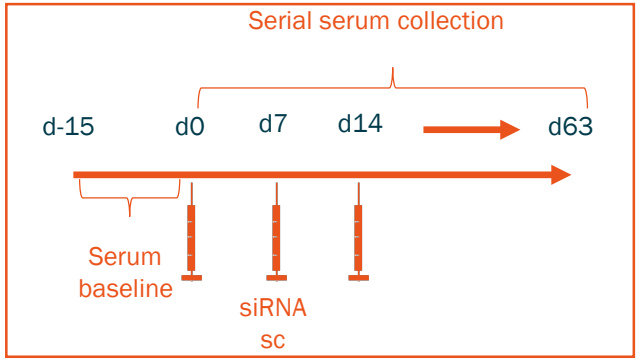
Sustained and Deep Lp(a) Knockdown Demonstrated in Animal Model

Serum Lp(a) reduction





Group	mg/kg	Days
1	0	0
2	3	1
3	9	1
4	3	1, 7, 14

Prolonged serum knockdown of Lp(a) in NHP

- Multiple dosing at 3mg/kg resulted in sustained reduction of Lp(a) serum levels (>90%) for at least over two months after first dose (max ~>95% KD)
- Similar outcome after single subcutaneous injection of SLN360 at 9mg/kg
- Over 85% KD at NADIR for single 3mg/kg injection with 50% KD still observed after 2 months post treatment

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SLN360 Summary

Rationale

- Lp(a) is a low-density lipoprotein produced predominantly by the liver and composed of Apo(a) and Apo B, both hepatocyte expressed genes.
- Genetically defined high Lp(a) serum levels are unaffected by diet and exercise and are an independent risk factor for CVD. There is no specific Lp(a) targeting therapy available at the moment.
- An *LPA* silencing siRNA would provide a specific, safe and durable approach for reducing Lp(a) levels in high risk patients.

Our Program

- A potent lead sequence has been selected and tested *in vivo* in non-human primates (NHP).
- Proof of mechanism has been achieved in NHP: dose dependent reduction in both LPA (liver mRNA) and Lp(a) (serum protein) observed, with max 95% KD observed after multiple dosing.
- Our drug compares positively against published data by competitors, suggesting a superior performance.
- **IND approved by FDA to start Phase 1 studies**

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SLN124
for the treatment of

Iron Overload Disorders



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Market Opportunity of SLN124

US and EU patients

β-Thalassemia

~40,000 TDT[1]
~20,000 NTDT[2]

Onset: from birth, but notable incidence of NTDT beyond 35

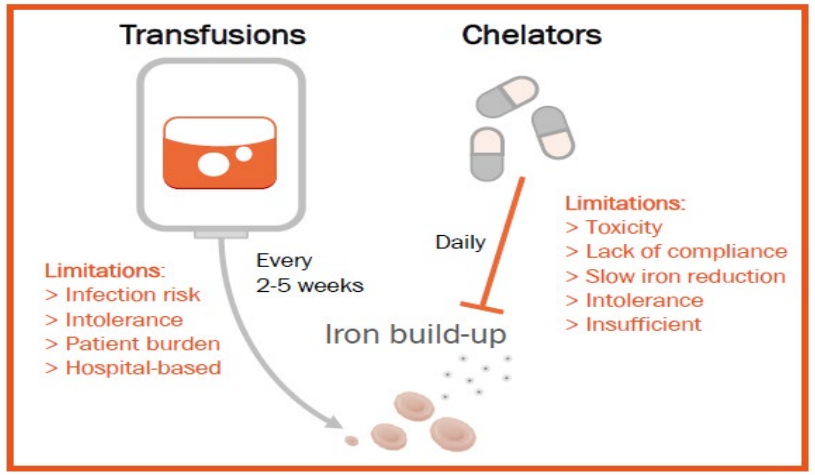
MDS[3]

>100,000

Onset: Typically >70y

Orphan indications

Standard of Care



Benefits of SLN124

SLN124 aims to:

1. Reduce organ iron levels &
2. Enhance erythropoiesis

↓

Reduced transfusion frequency &
Secondary iron overload burden

Advantages v Competition

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

Notes: 1 TDT = Transfusion Dependent Thalassemia 2 NTDT = Non Transfusion Dependent Thalassemia 3 MDS = Myelodysplastic Syndrome

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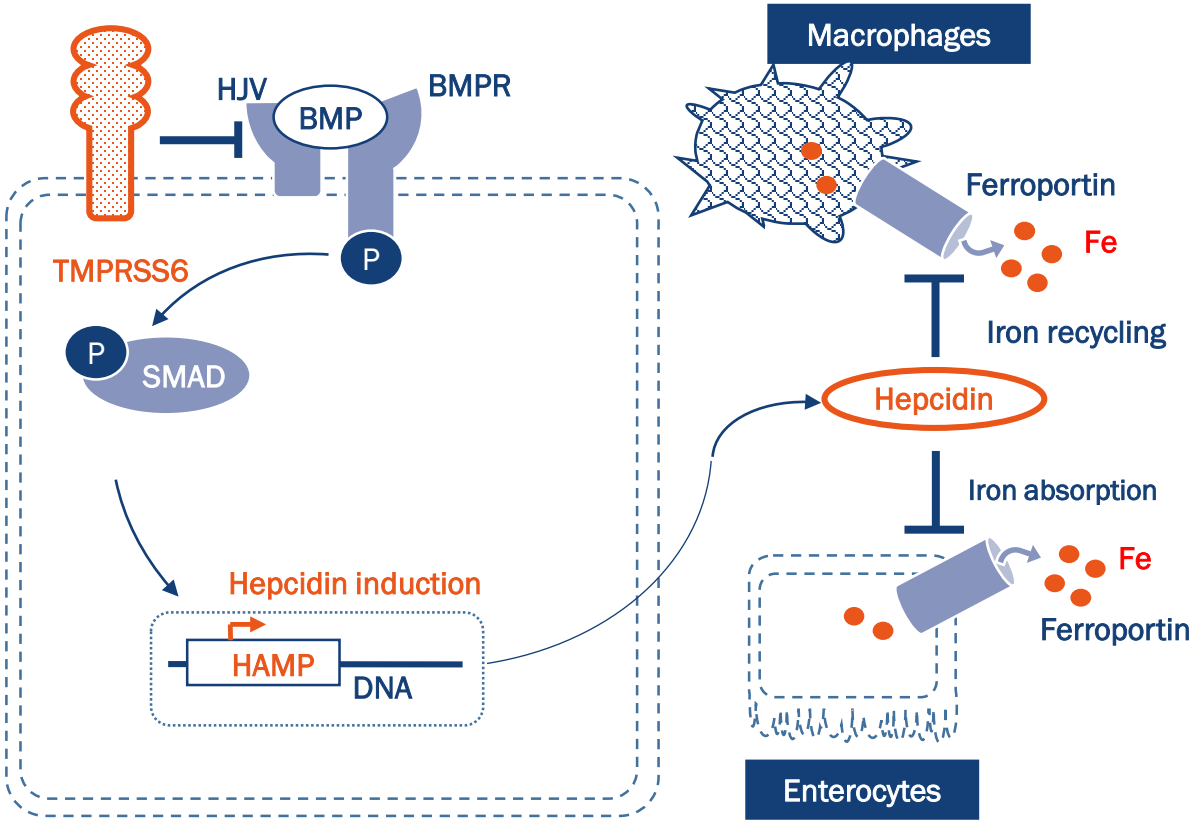
SLN124 Mechanism of Action: Increasing Hepcidin by Silencing its Repressor TMPRSS6



- **TMPRSS6** (Transmembrane Protease Serine 6) is a negative regulator of the BMP/SMAD signaling pathway
- Inhibition of TMPRSS6 in hepatocytes induces hepcidin expression
- Hepcidin reduces absorption of dietary iron and the release of iron from cellular storage, thereby reducing circulatory iron levels
- The liver is the predominant source of hepcidin

Silencing TMPRSS6

1. Increases hepcidin levels
2. Reduces iron levels
3. Improves erythropoiesis
4. Reduces anemia & iron overload

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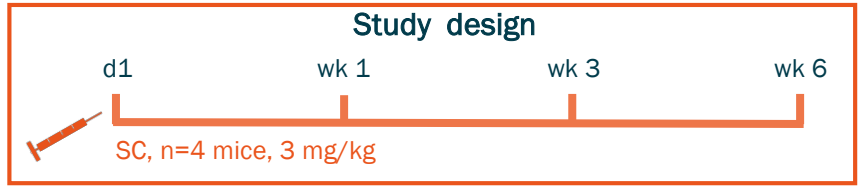
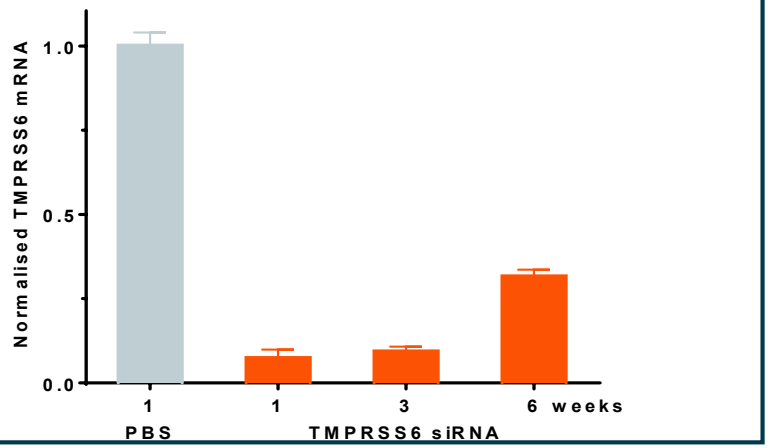
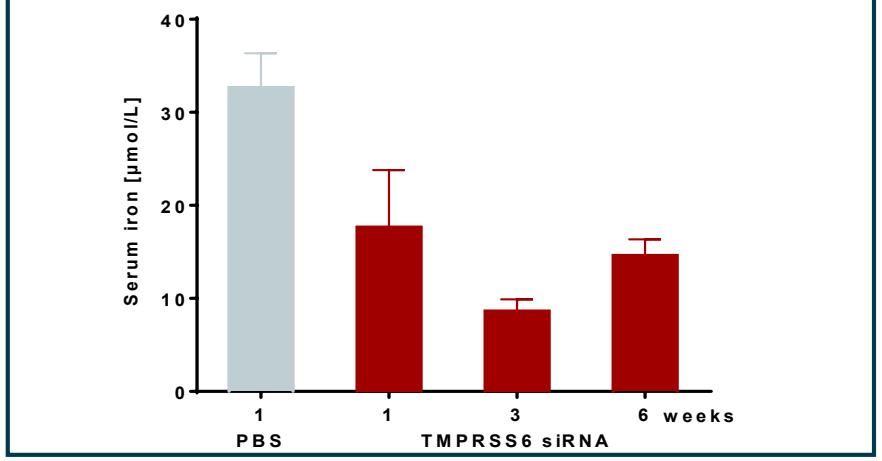
SLN124 Lowers Iron levels for at Least 6 Weeks After Single Administration in Mice



TMPRSS6 mRNA (liver)



Iron (serum)



- Long-lasting functional mRNA KD in liver
- Reduction of serum iron levels for at least 6 weeks
- Well tolerated with long duration of action in mice

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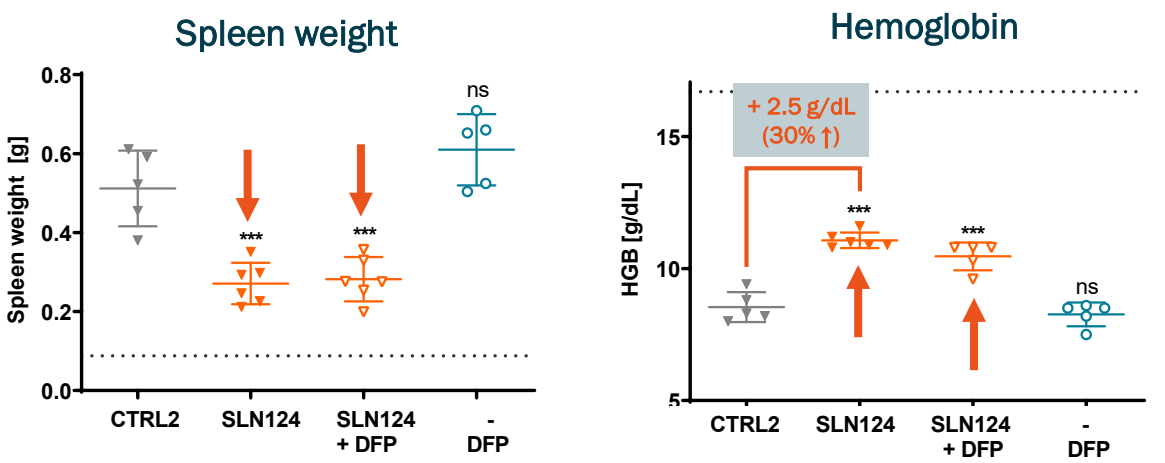
SLN124 Ameliorates Splenomegaly and Improves Anemia in β-Thalassemic Mice

Study design

Hbb$^{th3/+}$ mice, 2-4 m, n=5-8
2x 3mg/kg SLN124 s.c.
1.25 mg/ml deferiprone in drinking water



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



DFP = Deferiprone; CTRL2 = control siRNA

Levels of PBS-treated wild-type mice

- **Hb ↑ by ≥1.5 g/dL defined as "clinically relevant effect"**[1]
- No Δ Hb with 5-weeks DFP exposure
- ↓ need for blood transfusions by ↑ Hb (reflects 2-3 units of RBC)[2]

> SLN124 ameliorates splenomegaly; no impact by iron chelator DFP

> SLN124 improves anemia and ↓ the need for RBC transfusions

> No effect by DFP alone, SLN124 effect maintained in the presence of DFP

[1]Platzbecker et al., Blood 2019; [2]Bosch et al., Vox Sang 2017

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SLN500
for the treatment of

Complement-Mediated Diseases



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Complement as a Target Cascade

C3 - Hub of the complement cascade

>Complement belongs to the innate immune system

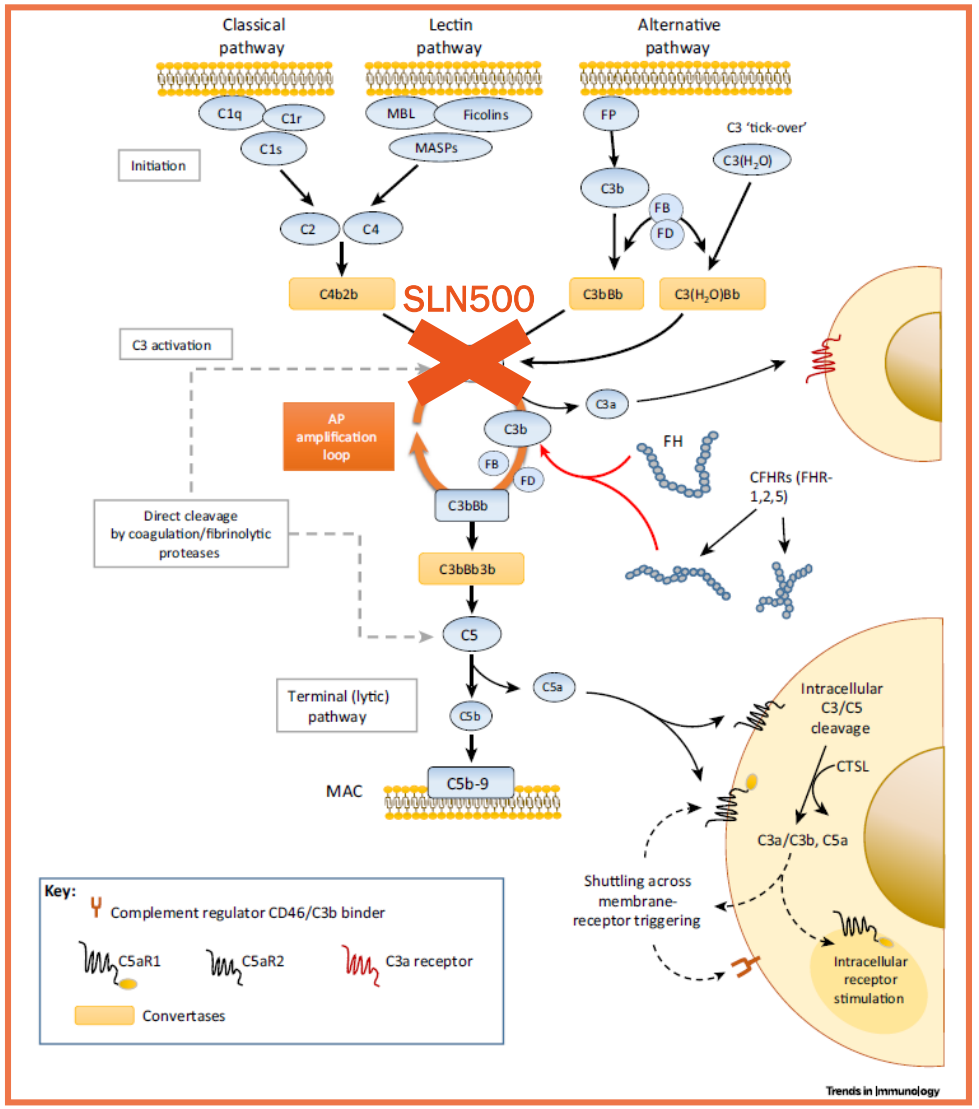
>Over 30 serum proteins

>Three pathways converge to form C3 convertases

>Function: MAC formation and immune cell activation

>Eculizumab (anti-C5 Ab): First FDA-approved drug for complement mediated diseases

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



MAC: Membrane attack complex

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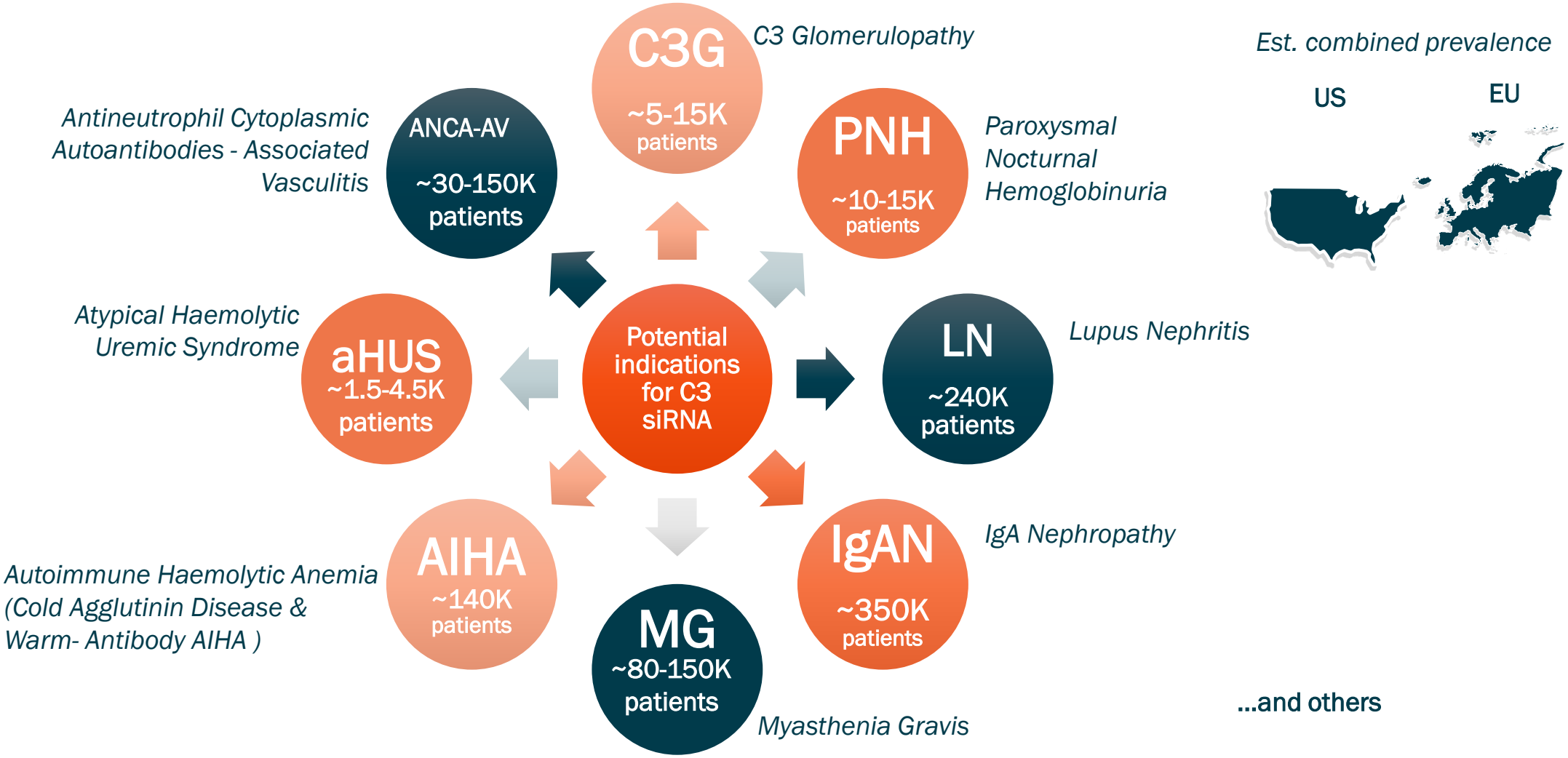
Attractive Market Size
Combined Opportunity in Multiple Orphan Indications



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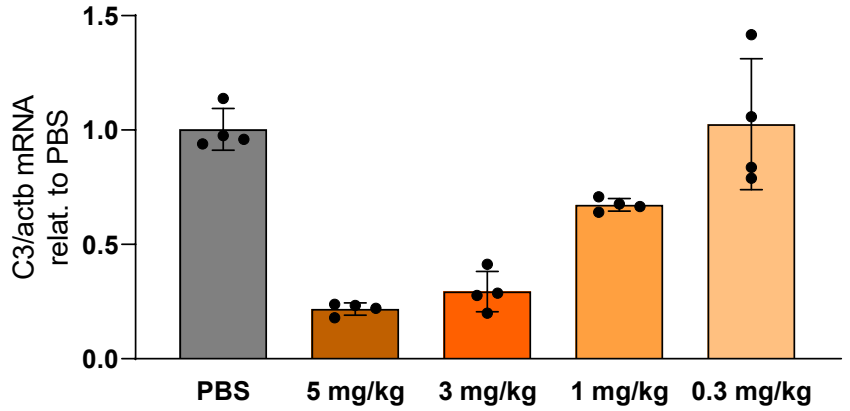
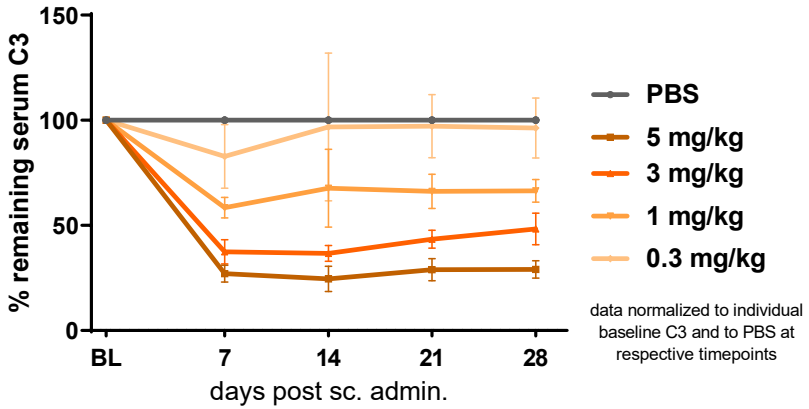
SLN500 Proof of Mechanism Data

Dose response study with SLN500 in healthy mice

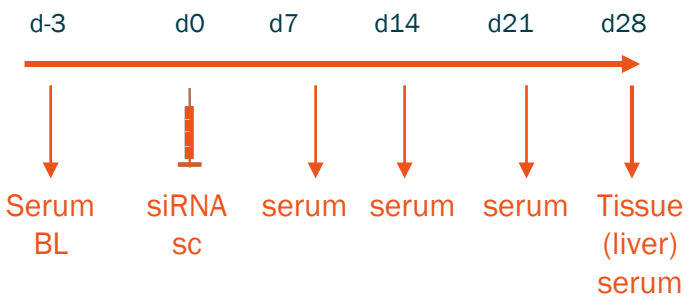
RNA DAY 28



PROTEIN TIME COURSE



> Study design:



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

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SLN500 Summary

Rationale

- Activation of the complement system is a pathologic feature of several diseases (such as C3 glomerulopathy, paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome and myasthenia gravis)
- Mutations and/or deficiencies in complement regulating factors or stabilizing autoantibodies of convertases are evident in patients with complement-mediated diseases
- C3 represents a hub in the complement cascade where all three pathways converge
- Blocking the complement cascade and its detrimental downstream effects is a promising therapeutic strategy

SLN500

- siRNA has significant advantages over other modalities, enabling potent and durable knock-down with a high therapeutic index, allowing for an improved dosing regimen for patients suffering from debilitating diseases
- Proof of mechanism has been achieved in mice: Dose-dependent reduction in both C3 mRNA and C3 serum protein was observed
- Collaborative deal signed with Mallinckrodt for C3 and up to 2 other complement targets

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Strong Experienced Team	> Pioneers in siRNA for over 18 years, growing clinical team, and experienced biopharma Board and Management team > Appointed experienced biopharma CEO – Mark Rothera – to lead next phase of growth
Target Selection	> Focused on targeting indications in rare diseases and large population targets, including new medicines for cardiovascular disease and complement-mediated diseases
Strong Financial Position	> Strong financial position with a cash runway extending beyond key clinical milestones such as SLN360 and SLN124 Phase 1 trial readouts

HQ in London



R&D in Berlin



+ New office in New York

Approx. 60 employees across all sites

Notes:
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