Development of a GalNAc-siRNA Conjugate Targeting TMPRSS6 for Treatment of Iron Overload

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Iron Overload in β–Thalassemia

• Mutations in HBB cause “stressed” erythropoiesis, hemolytic anemia & GI hyperabsorption of dietary iron
• Blood transfusions further enhance iron overload
• High iron levels worsen anemia and enhance dependency on blood transfusions
• Tissue accumulation of iron yields to organ damage & premature death

Medical Need:
➢ Reduce iron overload, improve erythropoiesis & reduce requirement for blood transfusions

Project Goal:
➢ Target a key modulator of iron homeostasis by GalNAc siRNA approach
Rationale for Targeting TMPRSS6

TMPRSS6 is a negative regulator of the BMP/SMAD signaling pathway; activation of the pathway induces Hepcidin expression.

Hepcidin reduces uptake of dietary iron and the release of iron from cellular storage.

Hepcidin levels are low in patients with iron loading anemias.

Inhibition of TMPRSS6 expression in the liver should raise Hepcidin and reduce iron absorption.

GalNAc siRNA approach for gene silencing in the liver.

Silencing TMPRSS6 in the liver increases Hepcidin expression, reduces systemic iron levels & improves erythropoiesis.
GalNAc siRNA Conjugate Inhibits TMPRSS6 Expression in 1° Hepatocytes by Receptor-Mediated Uptake

- Lead siRNA for TMPRSS6 identified (picomolar IC$_{50}$ by transfection)
- GalNAc siRNA conjugate is functional in 1° hepatocytes from different species (mouse, human, cynomolgus)
TMPRSS6 siRNA Conjugate is Functional in vivo (Mice)

- Study design:
  - d1: s.c. n=6
  - d4

→ POM: Silencing of TMPRSS6 in the liver induces Hepcidin expression and lowers serum iron levels in mice.
SLN124 Lowers Serum Iron Levels and Modulates Tissue Iron Distribution in Rodent Model for Hereditary Hemochromatosis

HFE−/− mice (6-8 wks)  n=6-7

Weeks 0 1 2 3

Prof. Muckenthaler Heidelberg University
SLN124 Normalises ROS and Improves RBC Parameters in β–Thalassemia Intermedia Disease Model (Hbb\textsuperscript{th3/+} Mice)

Hbb\textsuperscript{th3/+} mice (6-8 wks) n=3-6

SLN124 s.c.

Weeks 0 1 2 3 4 5

RBCs, Reactive Oxigen Species (ROS)

WT Hbb\textsuperscript{th3/+} Hbb\textsuperscript{th3/+}

ut Ctr SLN124

SLN124 Normalises ROS and Improves RBC Parameters in β–Thalassemia Intermedia Disease Model (Hbb\textsuperscript{th3/+} Mice)

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Summary & Conclusion

SLN124 a GalNAc siRNA conjugate targeting TMPRSS6 expression in the liver

> Highly potent, with durable activity by single s.c. application

> Lowers serum iron levels, transferrin saturation and reduces tissue iron accumulation in rodent model of hereditary hemochromatosis

> Normalises ROS in RBC, improves RBC parameter in rodent model for β-Thalassemia intermedia

> Is well tolerated in mice & NHP’s after single dose

> Non-Clinical Development and CMC has started in Q2/2017

> Start of Clinical Development is planned for Q4 2018

→ SLN124 represents a promising therapeutic candidate for patients with iron overload disorders, such as β-Thalassemia and Hereditary Hemochromatosis
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