SLN124, a GaINAc siRNA Conjugate Targeting TMPRSS6, for the Treatment of Iron Overload and Ineffective Erythropoiesis, such as in β-Thalassemia

1. Introduction

- Iron overload (IO) is a serious health condition, it leads to organ damage and dysfunction and serious clinical consequences including liver cirrhosis, heart failure, diabetes and growth retardation.
- In β-thalassemia IO is caused by frequent blood transfusions and by ineffective erythropoiesis and low Hepcidin levels, which mediate gastrointestinal iron hyperabsorption.
- In hereditary hemochromatosis iron overload is caused by a genetic defect in the hepcidin-ferroportin axis, which leads also to enhanced absorption of dietary iron and tissue iron accumulation.
- TMPRSS6 is a target gene involved in the regulation of Hepcidin expression and iron homeostasis.
- Here, we report on the pharmacological characterization of SLN124, a GaINAc siRNA conjugate targeting TMPRSS6, in preclinical models.

2. Rationale for targeting TMPRSS6

- TMPRSS6 is a negative regulator of the BMP/SMAD signaling pathway inducing Hepcidin expression.
- Hepcidin reduces uptake of dietary iron and efflux of iron from storage cells.
- Hepcidin levels are low in patients with iron loading anemias.
- Inhibition of TMPRSS6 expression in the liver will raise Hepcidin and reduce iron absorption.
- GaINAc siRNA approach for gene silencing in the liver.

3. SLN124 reduces TMPRSS6 mRNA expression in 1° hepatocytes from different species by receptor mediated uptake

4. Reduction of TMPRSS6 mRNA in the liver and serum iron levels in mice by single s.c. application

5. Therapeutic efficacy by SLN124 in rodent model for hereditary hemochromatosis type 1 (HFE/+) mice

6. Treatment of mice with established IO and in combination with Deferiprone

7. Therapeutic efficacy by SLN124 in rodent model for β-thalassemia Intermedia (Hbb°/° mice)

8. SLN124 reduces ROS and normalizes RBC maturation in Hbb°/°+ mice

9. SLN124 improves RBC maturation in bone marrow and spleen of Hbb°/° mice

10. Summary & Conclusions

- SLN124 is a highly potent siRNA conjugate for inhibition of TMPRSS6 expression and for modulation of iron homeostasis.
- Single s.c. injection of SLN124 is sufficient to lower TMPRSS6 expression and reduce systemic iron levels in vivo for several weeks.
- Demonstrated therapeutic efficacy in clinically relevant animal models for hereditary hemochromatosis type 1 and for β-thalassemia intermedia.
- Currently in preclinical development with plans to enter clinical development in 2019.