Development of HSD17B13 Targeting siRNA-GalNAc as a Potential Therapy for Fibrosis in NASH

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Nonalcoholic steatohepatitis (NASH) is one of the most common chronic liver diseases globally. It is characterized by steatosis (hepatic lipid accumulation), hepatocyte ballooning, lobular inflammation with increased risk of liver fibrosis. The progression of liver fibrosis to cirrhosis, hepatocellular carcinoma and end-stage liver disease is a key pathogenic factor for morbidity and mortality. Currently, no drug therapy has been approved for NASH management.

HSD17B13 is a lipid droplet associated protein that was recently identified as a potential therapeutic target for fibrosis in NASH. Human genetic studies have demonstrated that loss of function HSD17B13 mutants provide a protective effect against the development of liver fibrosis in the disease. We have therefore developed a siRNA-GalNAc conjugate, GNV069, to knockdown HSD17B13 as a potential therapy for liver fibrosis in NASH.

GNV069 comprises a potent siRNA that specifically recognizes and triggers the cleavage of the HSD17B13 mRNA and a proprietary GalNAc ligand that enables the effective delivery of this conjugate to hepatocytes through the ASGPR receptor. In vitro assessment demonstrated effective inhibition of HSD17B13 expression by GNV069 in both 2- and 3-dimensional culture of primary hepatocytes. An in vivo study in nonhuman primates (NHP) demonstrated 70% inhibition of HSD17B13 in the liver at Day 14 post a single 3 mg/kg dose. GNV069 was also well tolerated in both rat and NHP, providing a promising treatment for fibrosis in NASH.