The HBV siRNA, ALG-125755, demonstrates a favourable nonclinical profile and significant and durable hepatitis B surface antigen reductions in the AAV-HBV mouse efficacy model

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BACKGROUND AND AIMS
Currently approved therapies for chronic hepatitis B (CHB) infrequently achieve a functional cure in patients, which requires a sustained loss of hepatitis B surface antigen (HBsAg). In CHB patients, HBV targeted small interfering RNAs (siRNAs) have significantly reduced HBsAg, indicating a potential for their use in a curative therapeutic regimen. Here we evaluate the antiviral activity of ALG-125755, a N-acetylgalactosamine (GalNAc)-conjugated siRNA, in the adeno-associated virus (AAV)-HBV mouse efficacy model and its pharmacokinetic (PK) and safety profile in rats and monkeys.

RESULTS
Significant, Dose-Dependent, and Sustained HBsAg Reductions Observed in ALG-125755 Treated AAV-HBV Mice

ALG-125755 was Well Tolerated in Repeat Dose Toxicology Studies
Following 3 weekly doses SC, ALG-125755 was well tolerated up to the highest dose in rat (300 mg/kg/dose) and monkey (100 mg/kg/dose):
• No major changes in clinical chemistry, including ALT and AST, hematology or coagulation parameters
• Non-adverse, oligo-uptake related ALG-125755-related histopathology 2
• Vacular macrophages in lymph nodes and injection sites, basophilic granulates in renal tubules and hepatocytes, hepatocellular and renal tubular vacuolation

Dose-Dependent Increase in Plasma and Liver Exposures of ALG-125755

METHODS
In the AAV-HBV mouse model, various doses of ALG-125755 or vehicle were administered subcutaneously (SC) once b.i.w. for 10 weeks (6 doses) or monthly for 8 weeks (3 doses). For 24 weeks during dosing and follow-up, blood and liver samples were collected for plasma HBsAg and hepatitis B e antigen (HBeAg) assessments and liver ALG-125755 concentrations. The plasma samples were analyzed by LC-hybridization whereas the liver samples were analyzed by LC-MS for ALG-125755 concentration. For PK and toxicity studies, rats and monkeys were given single or weekly SC doses of ALG-125755 and plasma, liver and kidney were collected at various timepoints and analyzed for ALG-125755 concentrations by LC-MS.

REFERENCES