Pharmacodynamic durability of ALG-125755, a GalNAc-conjugated siRNA, correlated with total and RNA induced complex (RISC) bound siRNA in mouse liver

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BACKGROUND AND AIMS

For the functional cure of chronic hepatitis B, a sustained loss of hepatitis B surface antigen (HBsAg) is required. Targeted small interfering RNAs (siRNAs) have recently demonstrated significant clinical reduction of HBsAg. ALG-125755 is a novel N-acetylgalactosamine (GalNAc)-conjugated siRNA currently in clinical development. Here we demonstrate the mechanism of action of ALG-125755 and correlate the durable pharmacodynamics to total and RNA induced silencing complex (RISC) bound siRNA in mouse liver in the adenovirus-associated virus (AAV)/HBV mouse efficacy model.

METHOD

To confirm the mechanism of action of ALG-125755, argonaute-2 (AGO-2)-2 degradation of the target 5'-untranslated region (UTR) HBV RNA sequence induced by the antisense strand (AS), ALG-125736, was qualitatively measured using denaturing polyacrylamide gel electrophoresis. Total and RISC-bound siRNA quantification was performed in the harvested livers from a previously reported AAV-HBV mouse efficacy study, where a 10 mg/kg single dose or repeat doses up to 70 days at 1.5 or 5 mg/kg every other week (Q2W) or every four weeks (Q4W) demonstrated significant and durable decline in serum HBsAg. Weekly (Days 1-70) or bimonthly blood collection for HBsAg and HBsAg readouts. Liver samples (Days 14, 28, 70, each prior to the dose, and postdose timepoints at Days 96 and 186) from the single dose and repeat (Q2W) dose groups were analyzed by liquid chromatography-high resolution mass spectrometry (LC-HRMS) for detection of HBsAg and RISC-bound siRNA in the mouse livers 42 days following a single subcutaneous (SC) dose of ALG-125755 at 5 mg/kg.

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RESULTS

By 70 days post dose, the liver RISC-bound siRNA concentration increased with dose as measured by LC-HRMS. The increase in total and RISC-bound concentrations increased with dose as measured by LC-HRMS. The increase in total and RISC-bound concentrations increased with dose as measured by LC-HRMS.

CONCLUSIONS

• Binding of ALG-125755 to AGO-2 was demonstrated in vitro and in vivo, confirming that the mechanism of action for ALG-125755 is consistent with that of an siRNA

• Reductions in serum HBsAg levels was dose and dosing-regimen dependent and it was sustained for 270 days post-last dose ALG-125755 in AAV-HBV mice

• Pharmacodynamic response of HBsAg reduction and durability correlated with total siRNA and RISC-bound siRNA in mouse liver

• The long half-life of the RISC-bound siRNA in mice indicates that dosing of ALG-125755 in human could be less frequent than monthly dosing

• Clinical development of ALG-125755 as a potential best-in-class HBV siRNA is ongoing; dosing in healthy volunteers was initiated in October 2022, and dosing in CHB patients in December 2022

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