Incorporation of novel siRNA chemistries significantly improves the potency and durability of HBV siRNAs in the AAV-HBV mouse model

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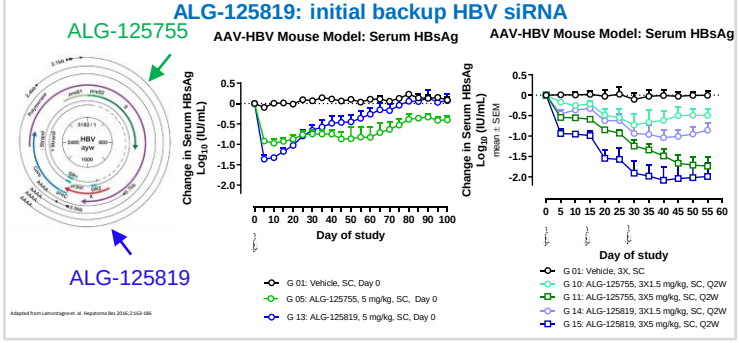
BACKGROUNDS

The current standard of care for chronic hepatitis B (CHB) fails to reduce HBsAg needed to attain functional cure. HBV siRNA therapies have been shown to be effective in reducing HBsAg in CHB patients. For decades, 2'F and 2'OMe modified nucleotides have been the building blocks used to stabilize siRNA duplexes and maintain RNA-like properties. In this study, we applied multiple novel stabilization chemistries, including 5' phosphate mimetic end cap and unique 2'F mimic nucleotides to distinct HBV siRNAs. As a result, we achieved significant improvements in the extent and duration of HBsAg knockdown in the serum of the AAV-HBV mouse model.

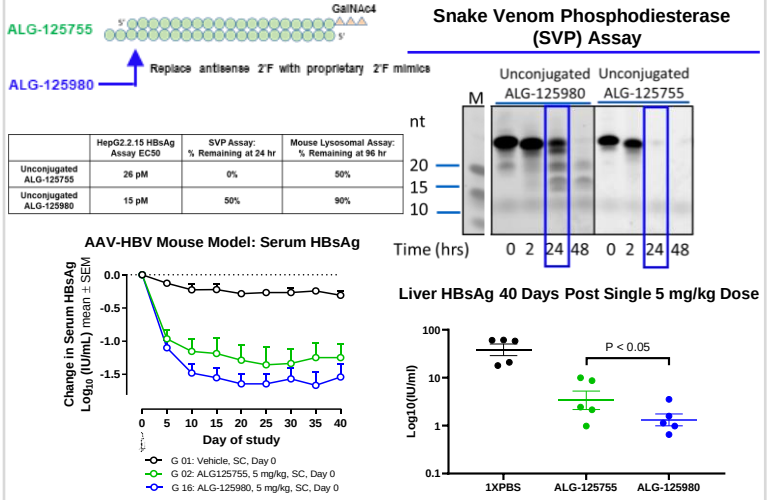
The stability of HBV siRNAs were profiled in lysosome and snake venom phosphodiesterase (SVP) assays. Human Ago-2 assay was used to assess siRNA loading and cleavage of target RNA. Inhibition of HBsAg release was performed in the HepG2.2.15 cell line by transfection using RNAiMAX. The secreted HBsAg was quantified by ELISA. In the AAV-HBV mouse model, HBV siRNAs conjugated with proprietary GalNAc were administered subcutaneously (SC) with blood collections every 5 days for HBsAg and ALT assessments.

RESULTS

ALG-125755: Aligos HBV siRNA in development
ALG-125819: initial backup HBV siRNA

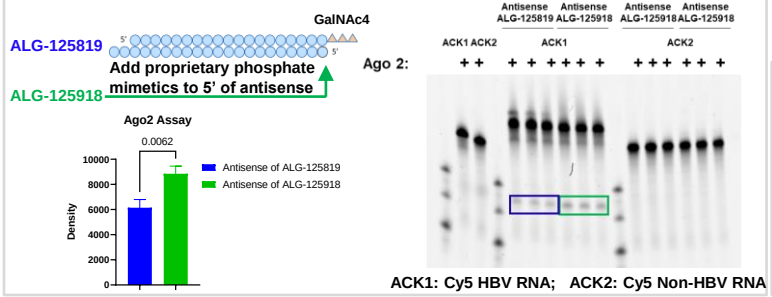


Proprietary 2'F Mimic Modified ALG-125755: Modestly Improved Nuclease Stability and In Vivo Potency



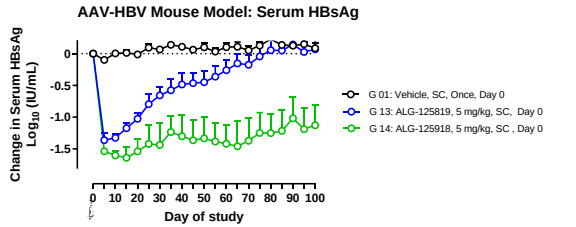
	HepG2.2.15 HBsAg Assay EC50	SVP Assay: % Remaining at 24 hr	Mouse Lysosomal Assay: % Remaining at 96 hr
Unconjugated ALG-125755	26 pM	0%	50%
Unconjugated ALG-125980	15 pM	50%	90%

Proprietary 5' End Cap Modified ALG-125819: Improved Ago-2 Activity

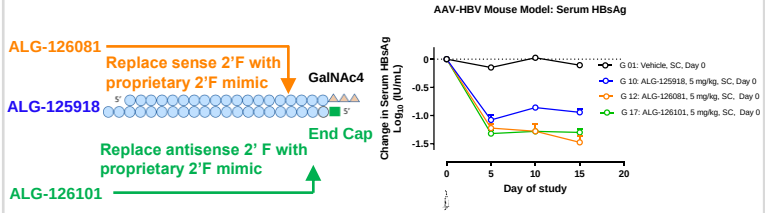


Results

ALG-125918 with Proprietary 5' End Cap Modification: Significantly Improved Maximum HBsAg Knockdown and Durability



Further Improvement in ALG-125918 with 2'F mimics



1) **Aligos proprietary phosphate mimetic end cap improved siRNA loading and cleavage efficiency and significantly improved in vivo target knockdown depth and durability.**

2) **Aligos proprietary 2'F improved siRNA nuclease stability and in vivo potency.**

3) **Combination of end cap and 2'F mimics yielded very potent HBV siRNA backup molecules ALG-126081 and ALG-126101.**