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.[1-4] 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.

METHODS

In the AAV-HBV mouse model, various doses of ALG-125755 or vehicle were administered subcutaneously (SC) once biweekly 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.

AAV-HBV MOUSE STUDY DESIGN

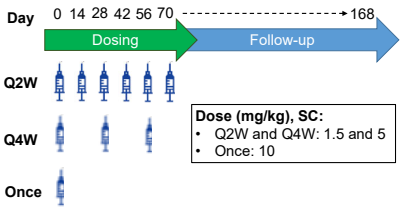


Figure 1. Dosing regimen and follow-up in AAV-HBV mouse study. *Syringes indicate SC dose on listed day. Q2W=biweekly, Q4W=every 4 weeks, and once=single dose. Dose levels for each regimen are indicated in the box.*

- Weekly blood collection during dosing and biweekly during follow-up for HBsAg and HBeAg assessments
- Liver* and plasma collection on Days 14, 28, 70, 98, 126 and 168 for ALG-125755 PK measurements

*Terminal liver samples collected from groups dedicated for PK analysis

RESULTS

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

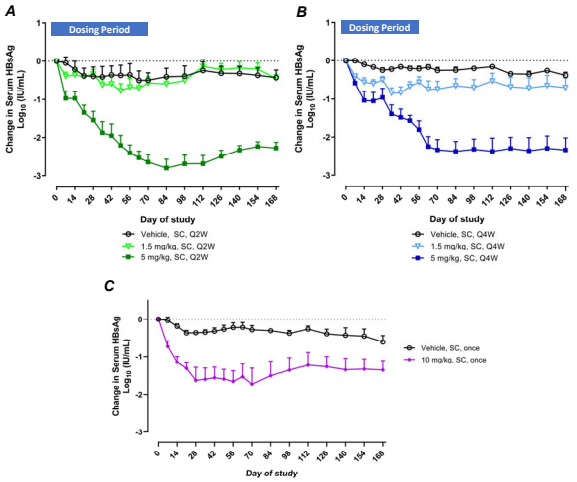


Figure 2. HBsAg reduction during dosing and follow-up in A) *Q2W dosing regimen groups* ***B)*** *Q4W dosing regimen groups and* ***C)*** *Single dose group.*

Mouse Liver Exposures of ALG-125755 Correlate with Reduction of Viral Antigens

Test Article	Dose (mg/kg/dose)	Dose Regimen	Maximum Mean Decrease in Serum Marker		Total siRNA* Mean Liver Concentration (µg/g) on Day 70
			HBsAg (Log_{10} IU/mL)	HBeAg (Log_{10} S/CO)	
Vehicle	0	All	-	-	-
ALG-125755	10	Once	1.7	0.60	0.56
	1.5	Q2W	0.78	0.23	4.77
	5	Q2W	2.8	1.2	17.8
	1.5	Q4W	0.85	0.25	2.86
	5	Q4W	2.4	0.89	12.2

*ALG-125755 + major active metabolite
HBsAg=Hepatitis B surface antigen, HBeAg=Hepatitis B e antigen, IU/mL=International units per milliliter, S/CO=Signal-to-cut-off

Table 1. Liver concentrations of siRNA are dose and dose-regimen dependent. *High liver concentrations correlate with greater HBsAg and HBeAg reductions, as with the 5 mg/kg/dose Q2W and Q4W groups.*

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)

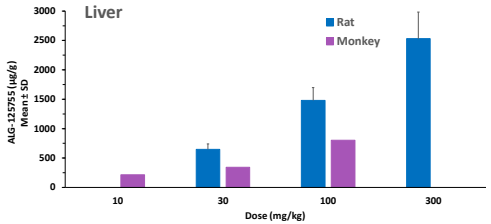
- No major changes in clinical chemistry, including ALT and AST, hematology or coagulation parameters
- Non-adverse, oligo-uptake related ALG-125755-related histopathology [5]:
  - Vacuolar macrophages in lymph nodes and injection sites, basophilic granulates in renal tubules and hepatocytes, hepatocellular and renal tubular vacuolation

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

ALG-125755 Mean PK Parameters	Rat				Monkey			
Dose regimen	Single*	3 Weekly Doses** Day 15			Single*	3 Weekly Doses** Day 15		
Dose (mg/kg/dose)	3	30	100	300	3	10	30	100
C_{max} (µg/mL)	0.34	8.91	29.1	80.1	0.33	2.47	8.74	27.3
AUC_{0-24} (µg·h/mL)	1.11	32.1	154	603	2.66	20.0	82.2	312

*Mean of males
**Sex-combined mean; Day 1 exposures not shown here were generally similar to the Day 15 exposures

Table 2. ALG-125755 PK parameters in rat and monkey plasma.



Concentration at 24 hours after the last dose in rat and 48 hours after the last dose in monkey.

Figure 3. Liver concentrations (male+female) of ALG-125755 in rat and monkey

- Increase in ALG-125755 plasma exposure was greater than (C_{max}) or nearly dose-proportional (AUC_{0-24})
- No accumulation; no sex difference
- High liver concentrations in rat and monkey following 3 weekly SC doses
- Kidney concentrations were significantly lower in monkey than rat

CONCLUSIONS

- A dose dependent inhibition of plasma HBsAg was observed with ALG-125755 in AAV-HBV mice
- Reductions in HBsAg levels were sustained for ≥70 days post-last dose
- Dose and dosing-regimen dependent exposures of ALG-125755 were observed in mouse liver and correlated with the pharmacodynamic effect
- Plasma exposures increased nearly or greater than dose proportionally
- High liver exposures of ALG-125755 were observed following single or repeated doses in rats and monkeys
- ALG-125755 was well-tolerated in rats and monkeys with no toxicologically relevant findings up to 300 and 100 mg/kg/dose, respectively
- Further development of ALG-125755 as a potential best-in-class HBV siRNA is ongoing; dosing in a Phase 1 study in healthy volunteers is anticipated in Q4 2022

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