

Nonclinical efficacy, pharmacokinetic profile and pharmacokinetic/pharmacodynamic (PK/PD) correlation of ALG-125755, a GalNAc-conjugated siRNA, for functional cure of chronic hepatitis B

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Background and Aim

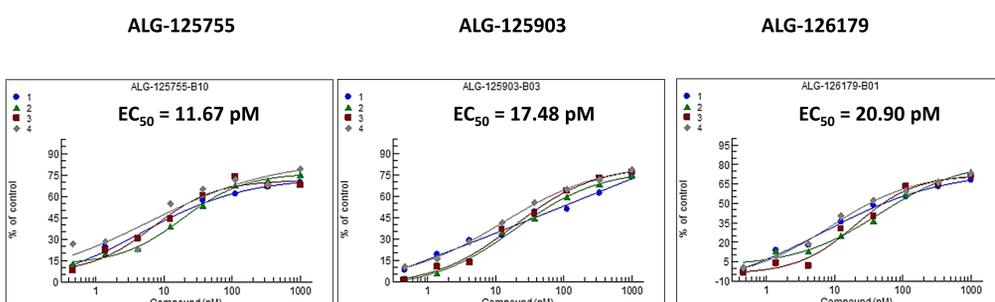
Chronic hepatitis B (CHB) is a major global health problem. The high morbidity and mortality associated with the disease emphasizes the need for a functional cure of CHB. We are developing ALG-125755, a N-acetylgalactosamine (GalNAc)-conjugated small interfering RNA (siRNA), with the aim of achieving sustained clearance of HBV surface antigen (HBsAg).

Methods

ALG-125755 and its metabolite, ALG-126144 (AS(N-1)3' ALG-125755), were tested in HepG2.2.15 cells infected with HBV Genotype D. PK parameters were obtained following a single short IV infusion at 1.5 mg/kg in monkey, a single subcutaneous (SC) dose at 5 to 15 mg/kg, or 6 weekly SC doses at 10 to 100 mg/kg/dose in rat and monkey. Compound metabolism was evaluated in vitro in plasma and mouse liver homogenate, and in vivo in rat and monkey plasma and tissues. Samples were analyzed by liquid chromatography (LC)-fluorescence detection or LC-mass spectrometry. PK/PD correlation was performed from a previously reported adeno-associated virus (AAV)-HBV mouse efficacy study where 10 mg/kg single dose, 5 mg/kg every other week or every four weeks demonstrated significant and durable decline in serum HBsAg (Fitzgerald et al Poster number SAT 386, EASL 2022). Steady state efficacious human liver concentrations were projected using a population PK model on the data from the in vivo efficacy study.

In vitro Activity of ALG-125755, ALG-125903 (Unconjugated ALG-125755) and ALG-126179 (Unconjugated Metabolite ALG-126144)

Figure 1. ALG-125755, ALG-125903 and ALG-126179 inhibition of HBsAg secretion in HepG2.2.15 Cells



In Vitro EC₅₀ and CC₅₀

- ALG-125755 and its unconjugated form ALG-125903 had comparable EC₅₀ values in the HepG2.2.15 cell line
- ALG-126179, the unconjugated form of metabolite ALG-126144 (AS(N-1)3' ALG-125755), demonstrated similar in vitro potency to the parent full length siRNA
- No cytotoxicity was observed (CC₅₀ >1000 pM for all siRNAs)

Pharmacokinetics Following a Single SC 5 mg/kg Dose in Rat and Monkey

Figure 2. Plasma and liver profile of ALG-125755 in rat and monkey

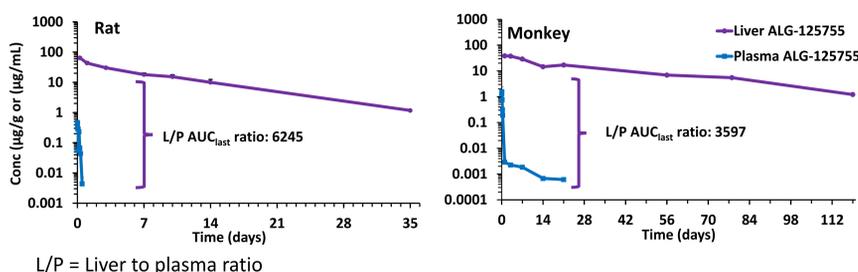


Table 1. Plasma and liver PK parameters of ALG-125755 in rat and monkey

Matrix	Rat			Monkey			F% ^a
	C _{max} (µg/mL or µg/g)	AUC _{last} (µg·h/mL or µg·h/g)	t _{1/2}	C _{max} (µg/mL or µg/g)	AUC _{last} (µg·h/mL or µg·h/g)	t _{1/2}	
Plasma	0.46	1.57	1.4 h	1.56	7.53	2.6 h	62.4
Liver	64.8	9807	6.8 d	38.4	27077	26.4 d	

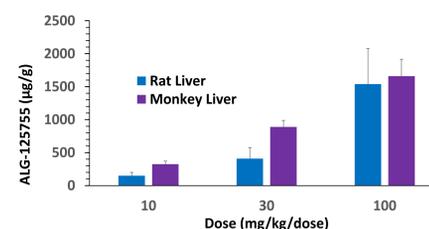
^aFrom AUC_{inf} following IV-infusion for 1 h at 1.5 mg/kg; h=hour, d=day; Plasma analysis by PNA hybridization method, Tissue analysis by LC-HRAM

Single SC Dose PK at 5 mg/kg

- Rapid absorption and distribution with short plasma half-life
- Good systemic bioavailability in monkey
- High liver to plasma ratio of ALG-125755
- Long half-life in liver supports at least monthly regimen in human

Liver Concentration Following Repeated SC Doses for 5 Weeks in Rat and Monkey

Figure 3. Liver concentrations of ALG-125755 in rat and monkey



Repeat SC Dose PK

- Five weekly doses up to 100 mg/kg/dose were well tolerated in rat and monkey
- No sex difference in plasma exposures or tissue concentrations
- Nearly or greater than dose-proportional increase, and no accumulation of plasma exposures of ALG-125755
- Rapid, efficient and dose-dependent uptake in liver in both species

Metabolism and Excretion

Metabolism

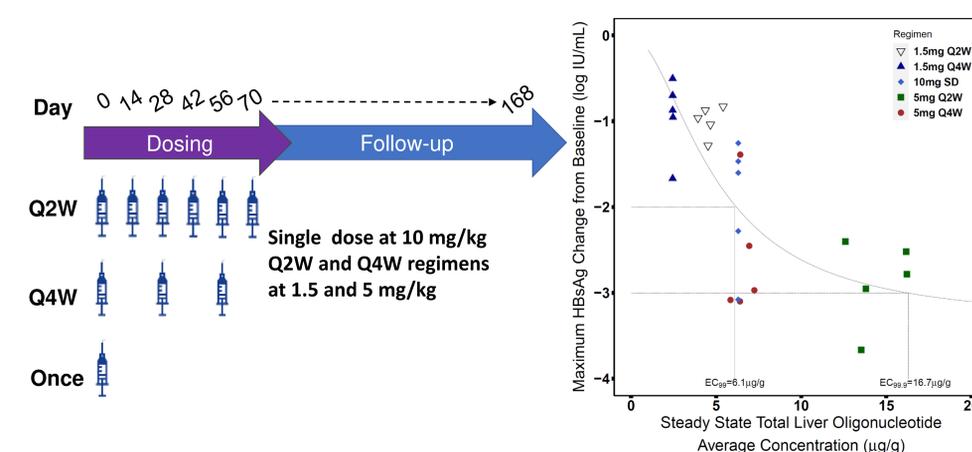
- In all rat and monkey matrices the sense strand, either as GalNAc conjugate or as full sequence with loss of GalNAc moieties and linkers to varying degree, was present suggesting that the oligonucleotide remained as a duplex
- The major analyte in liver and kidney was ALG-125755 and the major metabolite was ALG-126144. Minor metabolites of the antisense strand formed by the loss of up to 9 nucleotides from the 3'-end and up to 8 nucleotides from the 5'-end were noted in both tissues

Excretion

- Urinary excretion within 168 hours postdose of intact ALG-125755 and ALG-126144 was low, accounting for 0.069% of the administered dose in monkeys following a single SC dose

Pharmacokinetic/Pharmacodynamic Correlation in AAV-HBV Mouse Model

Figure 4. Correlation of liver concentrations at steady state to maximum HBsAg reduction



- A dose dependent inhibition of plasma HBsAg was observed with ALG-125755 in the model. Reductions in HBsAg levels were sustained for ≥70 days post-last dose (Fitzgerald et al Poster number SAT386, EASL 2022).
- Steady-state liver concentrations were projected using a population PK model based on sparse tissue concentrations of total siRNA for all dose groups
- Based on the analysis using a population PK and PK/PD I_{max} model, total liver oligonucleotides C_{avg} to achieve 99% (EC₉₉) and 99.9% (EC_{99.9}) HBsAg inhibition were projected to be 6.1 and 16.7 µg/g, respectively

Conclusions

ALG-125755 demonstrated desirable preclinical pharmacology and PK/PD properties, including a long liver half-life that favors monthly or less frequent dosing in human. ALG-125755 is being advanced into the clinic for the functional cure of CHB with anticipated dosing in healthy volunteers in Q4 2022.