Poster H-26

Preclinical Efficacy and Pharmacokinetics of ALG-010133, an S-Antigen Transport-inhibiting Oligonucleotide Polymers (STOPS™) for the Treatment of Chronic Hepatitis B (CHB)

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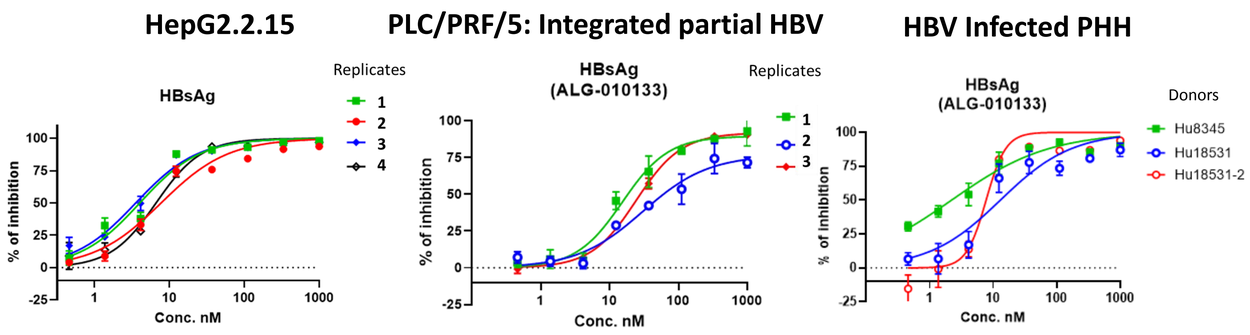
Background

Reducing or eliminating serum HBV S Antigen (HBsAg) is key to achieving functional cure in CHB patients. Nucleic acid polymers (NAPs) have been reported to reduce circulating HBsAg in patients with CHB by potentially affecting protein trafficking from the infected cell. S-antigen Transport-inhibiting Oligonucleotide Polymers (STOPS™) share structural similarities with NAPs but contain unique chemistries that improve in vitro potency. The objective of this project was to evaluate the preclinical in vitro efficacy and pharmacokinetics of ALG-010133, a STOPS™ molecule designed to reduce HBsAg levels in patients with CHB.

Methods

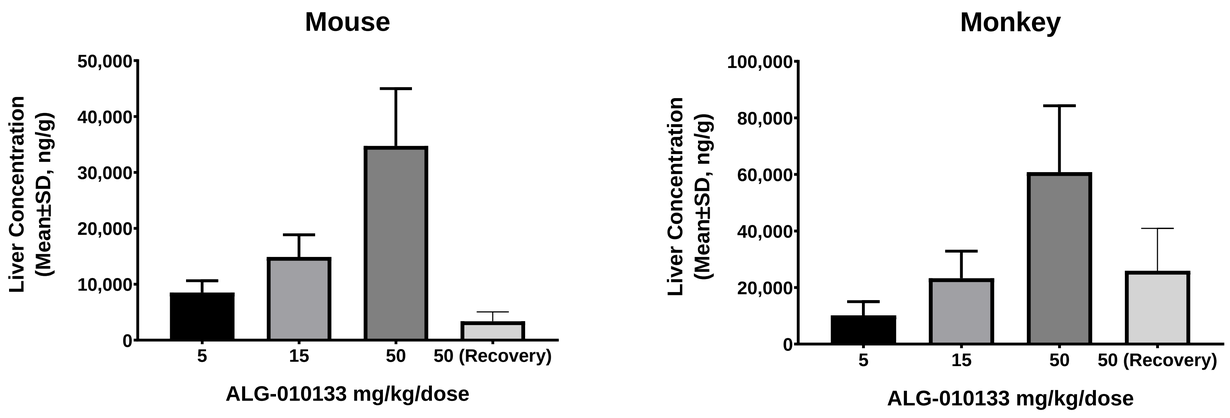
The effect of ALG-010133 on secreted HBsAg levels was assessed in HepG2.2.15, PLC/PRF/5, HepG2-GtA, HepG2-GtB, HepG2-NTCP (GtC and GtD) and HBV (GtD)-infected Primary Human Hepatocyte (PHH) systems. The pharmacokinetics of ALG-010133 was evaluated following single subcutaneous (SC) injections given to mice and monkeys or post 2-hour intravenous infusion (IV_{inf}) given to monkeys. ALG-010133 metabolites were qualitatively identified using LC-HRMS.

Potent inhibition of HBsAg secretion in in vitro assays



- ALG-010133 inhibited HBsAg release with EC_{50} values of 3.9, 23.7, 5.9, and 3.2 nM in HepG2.2.15, PLC/PRF/5, PHH (figures shown above) and HepG2-NTCP cells, respectively
- ALG-010133 inhibited HBsAg release in HepG2 cells containing genotype A, B, C and D genomes with EC_{50} values of 7.9, 9.25, 0.72 and 3.9 nM, respectively
- Intracellular HBsAg was concomitantly reduced (data not shown)

Dose-related increase in liver exposure following 3 weekly SC doses



ALG-010133 Tissue and Plasma Concentrations (Mean ± SD) Following 3 Weekly Doses SC

Species	Mouse			Monkey		
Dose (mg/kg/dose)	5	15	50	5	15	50
Liver* (µg/g)	8.5 ± 0.5	14.9 ± 0.9	34.7 ± 2.4	10.2 ± 2.0	23.3 ± 3.9	60.8 ± 9.6
Plasma AUC# (µg•h/mL)	0.8	6.6	37.7	29.9	122.0	368.0

#AUC_{0-6} and AUC_{0-24} were used for mouse and monkey respectively; *Mean of 2 and 6 hr for mouse and 48 hr for monkey following 3 weekly doses

- Greater than dose proportional increases in plasma exposure observed in both mice and monkey
- No accumulation was noted in plasma in either species following 3 weekly doses
- High and sustained concentrations achieved in liver following weekly dosing in both species
- The liver concentrations observed were in excess of in vitro antiviral EC_{90} values that are projected to be efficacious in humans
- Following 4-weeks of recovery, ALG-010133 concentrations decreased significantly in all tissues

Sustained exposure in liver following single SC dose in mice and monkeys

Species	Matrix	Dose (mg/kg)	Half-life (hour)	C_{max} (µg/mL or µg/g)	AUC_{last} (µg•h/mL or µg•h/g)
Mouse	Plasma	15	4	0.1	0.8
	Liver		91	15.7	930
Monkey	Plasma	5	NC	4	42
	Liver		147	13	1,078

NC: Not calculated due to insufficient points post C_{max}

- Rapid and high liver uptake was observed in mice and monkeys following single dose of ALG-010133
- ALG-010133 has a long half-life in liver, which supports once weekly dosing in humans. Overall, much higher exposure was seen in tissues compared to plasma

Minimal metabolites in plasma

- Pooled monkey plasma (n=10) following SC dose at 5 mg/kg were used for metabolite identification
- The parent compound was the most abundant species in plasma; only trace levels of 5'- exonuclease cleavage products (5'n-1 and 5'n-2) were observed

Limited urinary excretion in monkeys

- Following single SC dose of ALG-010133 in monkeys at 100 or 200 mg, ALG-010133 was quantifiable in urine up to the 60–72 hours post-dose time point
- 4% and 9% of dose were recovered in urine within 72 hours of ALG-010133 dose at 100 and 200 mg, respectively

Low potential for DDI

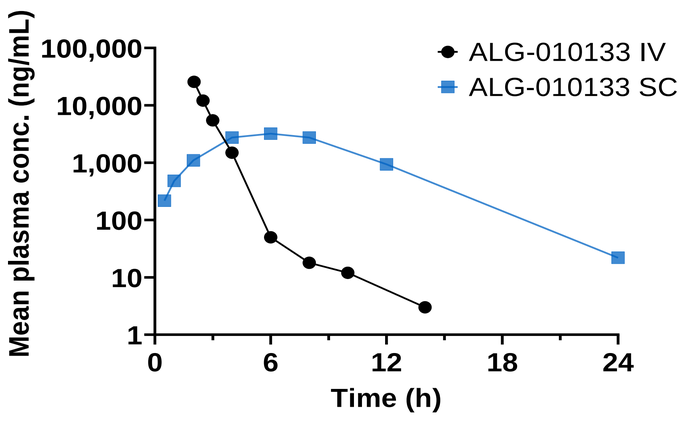
CYP450 Inhibition

- ALG-010133 exhibited low inhibition toward CYP450 isozymes with IC50 values >100 µM for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4

Transporter Inhibition

- No inhibition was observed for BCRP, p-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, and OATP1B3 at concentrations up to 100 µM

Good bioavailability following single SC dosing in monkeys



Dose (mg/kg)	Route	T_{max} (h)	C_{max} (µg/mL)	AUC_{0-24} (µg·h/mL)	$t_{1/2}$ (h)	Cl (mL/min/kg)	V_{ss} (L/kg)	F (%)
5	IV_{inf}	2	25.6	42.7	2.3	2	0.2	-
5	SC	6	3.2	26.2	2.3	-	-	62

- In monkeys, ALG-010133 had sustained plasma exposures and lower C_{max} with SC compared to IV dosing. SC dosing also showed good bioavailability (62-87%) across studies

Conclusions

The combination of excellent in vitro efficacy and a favorable pharmacokinetic profile has allowed ALG-010133 to advance into clinical development to be evaluated as a potential treatment for CHB.

References

1. Al-Mahtab et. al. PLOS ONE | DOI:10.1371/journal.pone.0156667 June 3, 2016
2. Bazinet et. al. Gastroenterology |DOI:10.1053/j.gastro.2020.02.058

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