THE S-ANTIGEN TRANSPORT-INHIBITING OLIGONUCLEOTIDE POLYMER (STOPS™) ALG-010133 DEMONSTRATES A FAVORABLE PRECLINICAL PROFILE FOR THE TREATMENT OF CHRONIC HEPATITIS B

AASLD November 13-16, 2020 The Liver Meeting® Digital Experience

Publication Number: 0831

Vikrant Gohil[1], Dinah Misner[1], Sushmita Chanda[1], Qingling Zhang[1], Jyanwei Liu[1], Jin Hong[1], Rajendra Pandey[1], Vivek K. Rajwanshi[1], Caroline Williams[1], Jeysen Yogaratnam[1], John Fry[1], David B. Smith[1], Julian A. Symons[1], Lawrence M. Blatt[1], Leonid N. Beigelman[1] and Tse-I Lin[2]

[1]Aligos Therapeutics, Inc., South San Francisco, CA; [2]Aligos Belgium BV, Leuven, Belgium, *Corresponding author: vgohil@aligos.com*

ALIGOS THERAPEUTICS

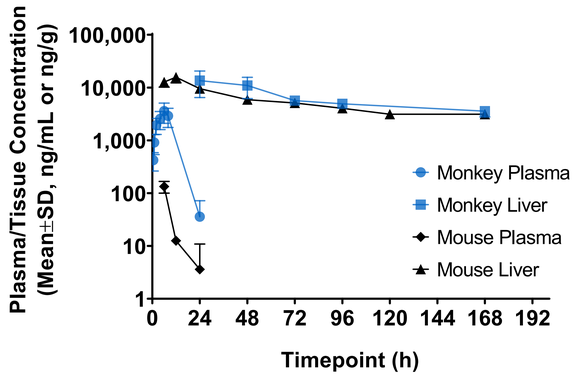
Background

Chronic Hepatitis B (CHB) viral infection is a global public health problem affecting over 290 million people. Current standard of care can effectively inhibit viral DNA replication but fails to reduce HBsAg. Nucleic acid polymers (NAPs) have been reported to reduce circulating HBsAg in patients with CHB by potentially affecting protein trafficking from the infected cell. We have identified STOPS™ compounds that contain several novel chemical features, providing enhanced potency in several HBV cell lines.

Methods

ALG-010133 was formulated in either phosphate buffered saline or water for injection. CD-1 mice and cynomolgus monkeys were dosed subcutaneously (SC), or by intravenous infusion (IV_{inf}) in monkeys, to assess the pharmacokinetic properties of ALG-010133. Additionally, toxicokinetic analysis was conducted in mice and monkeys administered ALG-010133 with weekly SC (QW; 3 doses) over 2 weeks in toxicology studies.

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

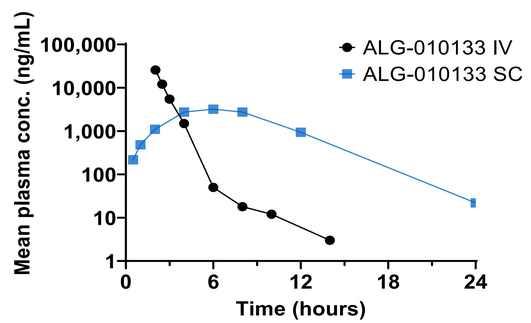


Species	Matrix	Dose (mg/kg)	Half-life (hour)	C_{max} (µg/mL or g)	AUC_{last} (µg•h/mL or g)
Mouse	Plasma	15	4	0.1	0.8
	Liver		91	15.7	930
Monkey	Plasma	5	NC	4	42
	Liver		147	13	1,078

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. Overall much higher exposure were seen in tissues compared to plasma
- Long half-life in the liver supports once weekly dosing in humans

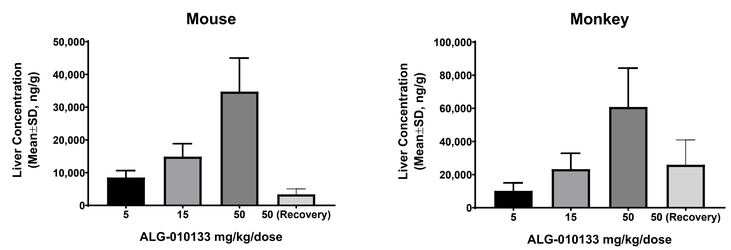
Good bioavailability following single SC dosing in monkeys



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	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%)

Dose-related increase in liver exposure following weekly SC dosing



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

Species	Mouse			Monkey		
Dose	5 mg/kg	15 mg/kg	50 mg/kg	5 mg/kg	15 mg/kg	50 mg/kg
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 weekly dosing for two weeks
- High and sustained concentrations achieved in liver following weekly dosing in both species
- Following 4-weeks of recovery ALG-010133 concentrations decreased significantly in all tissues

Minimal metabolites in plasma

- Pooled monkey plasma (n=10) following SC dose at 5mg/kg were used for metabolite identification; metabolites were qualitatively identified using LC-HRMS
- 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 hour 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 up to 100 µM

ALG-010133 demonstrated a favorable safety profile

- ALG-010133 was not mutagenic in the *in vitro* Ames assay
- ALG-010133 was not clastogenic in the *in vitro* or *in vivo* mouse MNT assays
- There were no cardiovascular, respiratory or CNS findings in safety pharmacology studies up to the highest doses tested of 50 mg/kg/dose
- In 2-week repeat dose studies in mice and monkey following weekly SC administration, ALG-010133 was well tolerated to up to the highest dose tested of 50 mg/kg/dose
  - There were no adverse changes in hematology, serum chemistry, coagulation parameters
  - There was no evidence of adverse cytokine or complement activation in either species
  - Minimal to mild histopathological changes were noted at the injection site, lymph nodes, liver and kidney were consistent with oligo-related uptake in these tissues
  - The no-observed-adverse-effect-level in both species was 50 mg/kg/dose, the highest dose tested

Conclusions

The combination of PK properties to enable SC administration along with a favorable safety profile allowed advancement of ALG-010133 into clinical development. ALG-010133 will be further 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

Financial disclosures: All authors are employees of Aligos Therapeutics, Inc.