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

Misner, DL[1], Gohil, V[1], Zhang, Q[1], Slater, C[2], Wojcinski, Z[3], Venkatraman, M[1], Chen, A[1], Rajwanshi, VK[1], Williams, C[1], Fry, J[1], Smith, DB[1], Symons, JA[1], Blatt, LM[1], Beigelman, LN[1], Lin, T[4] and Chanda, SM[1]

[1]Aligos Therapeutics, Inc.; [2]Charles River Lab.; [3]Tox. & Path. Consult., LLC; [4]Aligos Belgium BV, **Corresponding author: dmisner@aligos.com*

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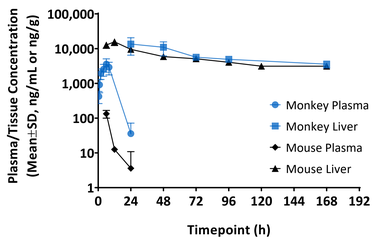
Background

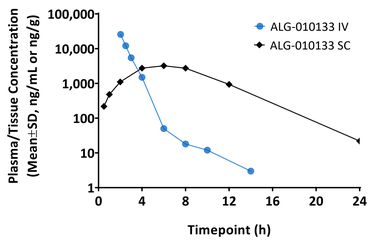
Current standard of care for CHB viral infection can effectively inhibit viral DNA replication but fails to reduce HBsAg. Nucleic acid polymers have been reported to reduce circulating HBsAg in CHB patients. We have identified STOPS that contain several novel chemical features, providing enhanced potency in several HBV cell lines.

Methods

ALG-010133 was generally formulated in 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. Repeat dose toxicology studies were conducted in mice and monkeys administered weekly (QW) SC for 2- or 13-weeks, and with twice weekly (BIW) dosing for 2 weeks followed by weekly dosing in 6- or 9-month chronic mouse or monkey toxicology studies, respectively. Reproductive toxicology studies were conducted in mice and NZW rabbits with twice weekly or every other day dosing.

Sustained ALG-010133 exposure in liver following a single SC dose in mice and monkey with good bioavailability following single SC dosing in monkeys





Species	Matrix	Dose (mg/kg; SC)	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}

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

- Rapid and high liver uptake was observed in mice and monkeys following a single dose
- Overall, much higher exposures were seen in tissues compared to plasma
- 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%)
- Long half-life in the liver supports once weekly dosing in humans

Low potential for DDI

- ALG-010133 exhibited low inhibition toward CYP450 isozymes with IC_{50} values >100 µM for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4
- No inhibition was observed for BCRP, p-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, and OATP1B3 up to 100 µM

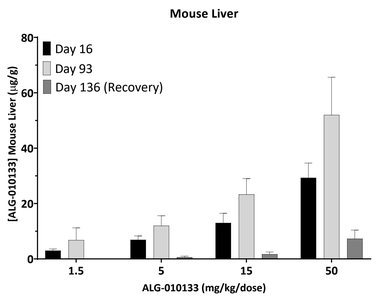
Minimal metabolites in plasma and limited urinary excretion in monkeys

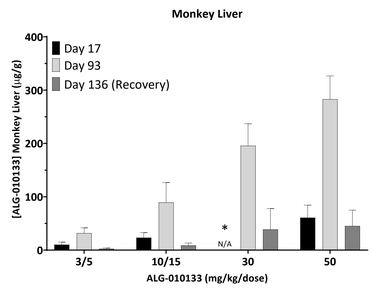
- Pooled monkey plasma (n=10) at 5mg/kg SC dose were used for metabolite identification using LC-HRMS
- The parent compound was the most abundant species in plasma; only trace levels of 5'- exonuclease cleavage products (5'n-1 and 5'n-2) were observed
- Following single SC dose of ALG-010133 in monkeys at 100 or 200 mg, ALG-010133 was quantifiable in urine up to 60–72 hours post-dose; 4% and 9% of dose were recovered in urine within 72 hour of ALG-010133 dose at 100 and 200 mg, respectively

ALG-010133 demonstrated a favorable safety profile

- ALG-010133 was not mutagenic in the *in vitro* Ames assay nor clastogenic in the *in vitro* or *in vivo* 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 and 13-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, cytokines, or complement activation (monkey only) in either species up to 50 mg/kg/dose
  - 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
  - In the 13-week study, the no-observed-adverse-effect-level (NOAEL) in mice decreased from 50 to 5 mg/kg/dose due to liver findings while the monkey NOAEL was maintained at 50 mg/kg/dose with no adverse findings noted

Dose- and time-related increase in mouse and monkey liver ALG-010133 exposures following weekly SC dosing through 13-weeks



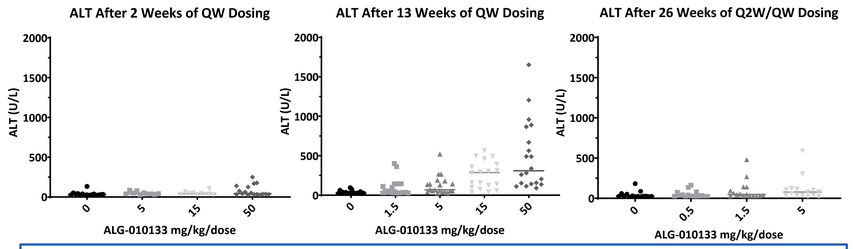


Species	Mouse (mg/kg/dose) 2-/13-week				Monkey (mg/kg/dose) 2-/13-week		
Dose	1.5	5	15	50	5/3	15/10	50
Liver* (µg/g)	3.0/6.8	6.9/12.0	13.0/23.3	29.3/52.0	10.2/31.7	23.3/89.4	60.8/282.9
Plasma AUC# (µg*h/mL)	2.9/3.9	9.2/17.0	126.1/172.5	1354/1661	29.9/15.2	122/79.7	368/428

*Concentration at 24 (mice) or 48 (monkey) hours; #Concentration at 6 hours (mice) in ng/mL

- High and sustained concentrations achieved in liver following weekly dosing in both species with ALG-010133 concentrations decreased significantly in all tissues following 2 to 8 weeks of recovery

Dose- and time-dependent increase of ALT observed in mice after 13-weeks at 15 and 50 mg/kg/dose but no significant ALT elevation in mice after 26-weeks up to 5 mg/kg/dose



- ALT elevations were noted at doses ≥15 mg/kg/dose in mice that were reversible after 6 weeks of recovery
- With longer-term dosing through 26 weeks, ALT elevations did not progress nor was there any evidence of liver toxicity histologically up to 50 mg/kg/dose nor were there changes up to 50 mg/kg/dose in NHPs through 39 weeks of dosing

Species	Mouse (mg/kg/dose)			Monkey (mg/kg/dose)		
Dose	0.5 mg/kg	1.5 mg/kg	5 mg/kg	5 mg/kg	15 mg/kg	50 mg/kg
Liver* (µg/g)	4	9.6	19.9	84.4	636.5	1360
Plasma AUC# (µg*h/mL)	N.D.	N.D.	N.D.	59.9	220.6	668.5

*Concentration at 24 (mice) or 48 (monkey) hours after last dose; #Day 1; N.D. = not determined

- NOAELs were 5 mg/kg/dose in 6-month mouse repeat dose study and 50 mg/kg/dose in 9-month repeat dose monkey study, the highest doses tested

No adverse findings in embryofetal development or fertility studies noted

- No significant findings noted on either male or female mouse fertility or early embryofetal development when dosed either twice weekly (males) or every other day (females) up to 50 mg/kg/dose
- No effects observed in a mouse preliminary embryofetal development study when dosed every other day up to 50 mg/kg/dose
- Female rabbits had decreased body weights and/or body weight gains were noted at dose levels ≥15 mg/kg/dose and at liver exposures higher than those achieved in monkey repeat-dose toxicity studies
- No effects observed in a rabbit preliminary embryofetal development study when dosed every other day up to 10 mg/kg/dose

Conclusions

The combination of PK properties to enable SC administration along with a favorable safety profile allowed advancement of ALG-010133 into clinical development to be evaluated as a potential treatment for CHB. The lack of efficacy after 12-weeks of dosing in CHB subjects resulted in the termination of ALG-010133 for CHB treatment.

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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