Safety, Tolerability and Pharmacokinetics (PK) of Single and Multiple Doses of ALG-010133, an S-antigen Transport Inhibiting Oligonucleotide Polymer (STOPS™), for the Treatment of Chronic Hepatitis B

E. Gane[1], MF Yuen[2], A Jucov[3] J Yogaratnam[4], K Le[4], J Vuong[4], C Westland[4], V Gohil[4], C Schwabe[5], K Agarwal[6], J Liu[4], T Lin[4], L Blatt[4], S Chanda[4], M McClure[4], J Fry[4]

[1]University of Auckland, New Zealand; [2]University of Hong Kong, Hong Kong; [3]Nicolae Testemitanu State University of Medicine and Pharmacy, Moldova; [4]Aligos Therapeutics, United States; [5]Auckland Clinical Service, New Zealand; [6]Institute of Liver Studies, Kings College Hospital, London, United Kingdom

INTRODUCTION

Chronic Hepatitis B (CHB) affects >250 million people worldwide and complications of CHB are associated with an annual mortality rate of ~900,000/year (WHO HBV fact sheet 2020). Despite its significant impact on global health, the current standard of care for CHB, nucleos(t)ide analogs, rarely results in functional cure, the goal of CHB treatment. There is a significant unmet medical need for CHB treatments which can enhance functional cure rates. ALG-010133 is an S-antigen Transport Inhibiting Oligonucleotide Polymer (STOPS™) molecule which, in vitro, substantially reduces Hepatitis B surface antigen (HBsAg) production and release from infected hepatocytes with single digit nM potency. ALG-010133 has been demonstrated to act synergistically with other anti-HBV drugs and is being developed for inclusion in a combination regimen to achieve higher rates of functional cure in CHB.

AIM

To evaluate the safety and PK of subcutaneously (SC) administered ALG-010133 in healthy volunteers (HVs).

METHODS

This is a three-part, multicenter, double-blind, randomized, placebo-controlled study:

- Part 1 was a single ascending dose (SAD) study and Part 2 was a multiple ascending dose (MAD) study. Parts 1-2 evaluated the safety and PK of single or multiple (3 weekly) SC doses, respectively, of ALG-010133/placebo in HVs
- Each cohort consisted of 8 HVs who were randomized to ALG-010133 or placebo in a 3:1 ratio
- Throughout study conduct, safety assessments (adverse events (AEs), vital signs, electrocardiogram (ECG) and laboratories) and plasma/urine PK samples were collected and analyzed.

PK-PD modeling

- Used human PK data combined with monkey plasma/liver PK data, which were assumed to predict human liver exposures
- Assumed >10-fold EC_{50} total ALG-010133 concentration for inhibition of HBsAg secretion at steady state in the liver was required for antiviral activity (pharmacodynamic (PD) effect).
- Was based on PK simulations over a range of doses using individual PK parameters of subjects and body weight ranges to predict the efficacious dose range.

For clinical data, subjects receiving the same dose (placebo or 200 mg) were pooled. Continuous data are presented as mean (standard deviation(SD)). Categorical data are presented as percentages.

Reported here are preliminary safety and PK results from Parts 1-2

RESULTS

DOSE LEVELS EVALUATED*

- In the SAD, across 7 cohorts, the following single SC doses were evaluated: 20, 50, 75, 125, 200, 160, 200 mg
- In the MAD, across two cohorts, three weekly SC doses at the following levels were evaluated: 120, 180 mg

*All doses were given using 100 mg/mL solution, except SAD cohort #7, which used a 200 mg/mL solution

BASELINE CHARACTERISTICS

The baseline characteristics were generally well balanced across treatment groups and typical for a HV population

	SAD							MAD		
Dose (mg)	20	50	75	125	160	200	Placebo	120	180	Placebo
N	6	6	6	6	6	12	14	6	6	4
Age, years (mean (SD))	33.7 (7.9)	31.3 (11.4)	29.0 (5.7)	27.3 (2.6)	29.7 (12.8)	31.3 (7.6)	29.8 (12.3)	33.3 (8.1)	23.0 (4.2)	30.8 (10.5)
% Male	100%	100%	100%	100%	100%	100%	86%	100%	100%	100%
% White	50%	50%	33%	33%	66%	75%	71%	83%	66%	75%
BMI, kg/m^2 (mean(SD))	24.8 (3.4)	24.3 (2.8)	24.4 (2.4)	25.2 (1.3)	23.9 (4.0)	25.7 (3.8)	24.7 (3.8)	25.6 (3.2)	23.3 (3.1)	27.4 (4.6)

PK - SAD

- Plasma ALG-010133 exposures increased in a greater than dose proportional manner at low doses and approached linearity with doses above 125 mg. Mean $t_{½}$ was 3.3 to 8.3 hours and there was moderate inter-subject variability (22-60% CV for AUC). Bioavailability increased with higher doses as evidenced by correlated decreases in both CL/F and V/F

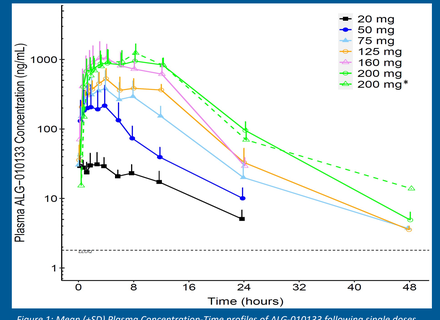

Figure 1: Mean (+SD) Plasma Concentration-Time profiles of ALG-010133 following single doses

Dose* (mg)	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}24h}$ (ng.hr/mL)	$AUC_{0\text{-}INF\_obs}$ (ng.hr/mL)	$t_{1/2}$ (hr)	CLss_F (L/hr)	Vz_F (L)
20	33.7 (39.0)	3.5 (0.5,12)	392 (21.8)	427 (29.2)	8.3 (3.2)	46.8 (30.5)	520 (41.9)
50	171 (95.4)	2 (1,4)	1480 (59.8)	1630 (52.1)	6.3 (3.9)	30.7 (42.2)	226 (89.0)
75	382 (64.8)	4 (1.5,8)	3560 (44.6)	4460 (33.6)	4.1 (2.2)	16.8 (37.6)	89.9 (87.5)
125	511 (38.5)	4 (4,12)	5980 (22.5)	6140 (22.0)	4.4 (1.5)	20.4 (20.4)	122 (48.8)
160	989 (60.4)	3.5 (3,12)	10,700 (45.1)	12,300 (43.7)	3.3 (0.7)	13.0 (41.0)	61.5 (60.1)
200	1030 (37.0)	10 (3,12)	13,200 (29.5)	17,200 (3.3)	3.9 (1.1)	11.6 (3.3)	64.8 (25.6)
200*	1170 (35.8)	8 (6,12)	13,500 (31.5)	13,500 (44.5)	6.3 (3.8)	14.9 (44.5)	123 (91.9)

*All doses were given using 100 mg/mL solution, except SAD cohort #7, which used a 200 mg/mL solution; Values represent Geometric Mean (Coefficient of Variation [CV]%), except T_{max}: median (minimum, maximum) and $t_{1/2}$ which is average (SD).

PK - MAD

- No plasma accumulation with weekly dosing (AUC ratio = 0.92 [90%CI=0.81-1.03])

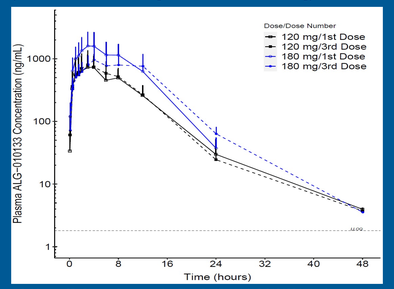

Figure 2: Mean (+SD) Plasma Concentration-Time Profiles of ALG-010133 following multiple doses

Dose (mg)	Dose Number	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}24h}$ (ng.hr/mL)
120	1st Dose	669 (56.4)	4 (1,8)	6700 (33.1)
120	3rd Dose	736 (61.7)	3.5 (3,8)	7060 (37.8)
180	1st Dose	1360 (66.3)	4 (3,8)	14,300 (47.3)
180	3rd Dose	920 (56.9)	4 (3,12)	11,200 (44.9)

Values represent Geometric Mean (Coefficient of Variation [CV]%), except Tmax: median (minimum, maximum)

PK - PD

- Weekly SC doses of ≥ 120 mg are expected to achieve steady-state liver ALG-010133 concentrations >10-fold EC_{50} and are projected to have antiviral activity in CHB subjects

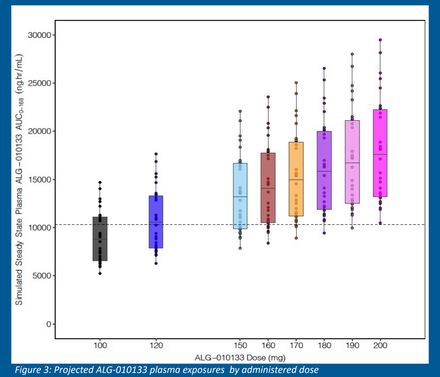

Figure 3: Projected ALG-010133 plasma exposures by administered dose

Dots represent simulated PK with different doses for individual study subjects. Boxes represent first and third quartiles (25th and 75th percentiles); line within each box represents median (50th percentile). Whiskers extend to the largest value no further than 1.5 * interquartile range from the hinges. The dotted line represents the mean efficacious plasma exposure needed to achieve total liver concentrations >10-fold EC_{50} for HBsAg in a 90 kg subject.

SAFETY

Single and multiple ALG-010133 doses were generally well tolerated

- No serious adverse events
- Treatment emergent adverse events (TEAEs)
  - No TEAEs led to study drug discontinuation
  - The most common TEAEs (≥3 subjects) and their severities are reported in the table. There was no evidence of a clinically significant dose response in the incidence of TEAEs

	SAD							MAD		
Dose (mg)	20	50	75	125	160	200	Placebo	120	180	Placebo
N	6	6	6	6	6	12	14	6	6	4
Headache	1	1	0	1	1	2	6**	1	0	0
Injection site reaction (ISR)	0	0	3*	2**	0	2*^	0	1*	2	0
Injection Site Bruising	0	0	1	2	2	5	1	0	1	0
Diarrhea	1	1	0	0	0	1	0	0	0	2
Venipuncture site bruising	0	1	0	0	0	0	1	0	0	1
Nausea	0	0	1	0	1	0	1	0	0	0
Abdominal pain/discomfort	0	0	0	0	0	1	1	0	1	0

Each * and ^ symbol represents a single subject experiencing a moderate or severe event, respectively. All other subjects experienced mild events

- ISRs occurred in ~19% of ALG-010133 treated subjects. They were generally characterized by localized erythema that was mild to moderate in severity and resolved over time. One SAD ISR was considered severe based on surface area criteria (>100 cm^2)
- All TEAEs that occurred in 1-2 subjects were mild in severity

- No clinically concerning laboratory, ECG, vital sign or physical examination findings

CONCLUSIONS

ALG-010133 was safe and generally well tolerated after single and three weekly doses in HVs. Exposures increased greater than dose proportionally and doses ≥120 mg are projected to have antiviral activity. In Part 3, 120 mg is being evaluated in patients with CHB.

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CONTACT Matt McClure - mmcclure@aligos.com