Poster H-20

Excellent preclinical characteristics of ALG-000184, a prodrug of the HBV capsid assembly modulator ALG-001075

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Background

The hepatitis B virus (HBV) capsid assembly process has emerged as a key target for the treatment of chronic hepatitis B. Capsid assembly modulators (CAMs) affect HBV core protein assembly into aberrant structures (class-I) or empty capsids (class-II), inhibiting HBV RNA encapsidation.[1] Aligos is advancing multiple structurally diverse CAMs from both classes. We recently reported on ALG-001075, a novel class-II CAM with potent and broad-spectrum antiviral activity.[2] ALG-000184, a prodrug of ALG-001075 with excellent pharmacological properties is currently in Phase 1 clinical testing.[2] Here, we describe the antiviral activity of ALG-001075 in an HBV-DNA log drop assay, the in vivo activity in the AAV-HBV mouse efficacy model and the potential for drug-drug interactions.

Methods

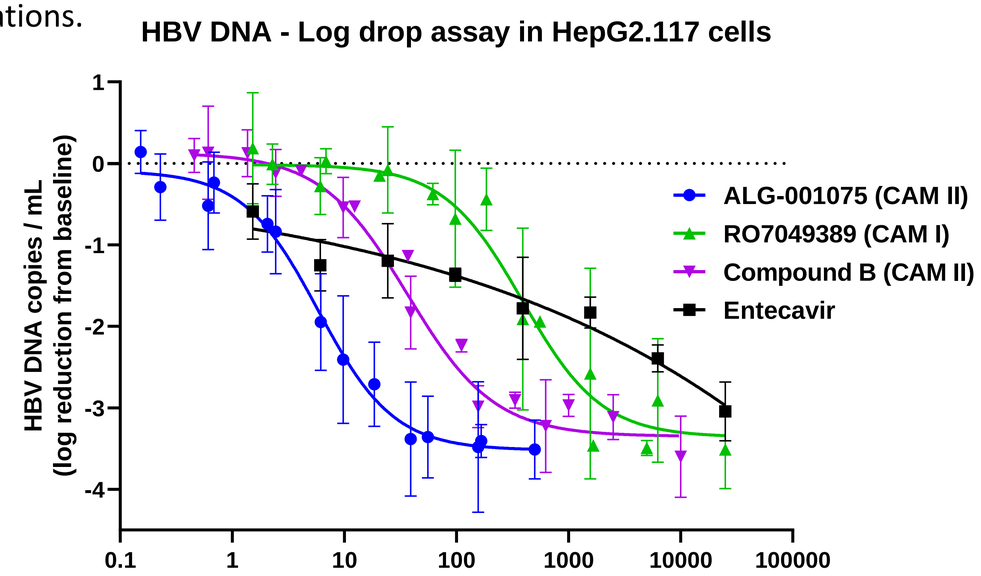
Cell-based antiviral activity was measured via qPCR. Encapsidated HBV DNA was specifically detected by including DNase digestion of cell lysates to reduce background integrated HBV DNA. The in vivo activity was determined in the AAV-HBV mouse infection model. ALG-000184 and ALG-001075 were evaluated in vitro for their drug-drug interaction potential related to cytochrome P450 (CYP) and transporters. Entecavir, the class II CAM compound B from patent application WO2019175657 and the class I CAM RO7049389 were used as comparators.

Results 1 - In Vitro Antiviral Activity

In order to understand the magnitude of the antiviral activity of ALG-001075, the parent molecule of ALG-000184, we determined the amount of encapsidated viral DNA in HepG2.117 cells and calculated the EC_{50}, EC_{90}, EC_{99} and $EC_{99.9}$. ALG-001075 reduced encapsidated DNA by up to 3.5 log_{10} copies/ml and with an $EC_{99.9}$ of 29.0 ± 29.9 nM in this log-drop assay (**Table 1 and Figure 1**). Entecavir displayed incomplete inhibition, even at high concentrations.

	EC_{50}	EC_{90}	EC_{99}	$EC_{99.9}$
	nM; mean ± SD, n ≥ 2			
ALG-001075 (CAM II)	1.01 ± 0.64	3.09 ± 1.90	8.11 ± 4.65	29.02 ± 29.86
Entecavir (nucleoside)	< 1.5	7.27 ± 4.11	1712 ± 1576	17800
RO7049389 (CAM I)	92.02 ± 60.49	304.1 ± 217.2	1099 ± 1268	3871 ± 5267
Compound B (CAM II)	6.62 ± 2.30	20.15 ± 7.01	54.20 ± 20.62	355.2 ± 322.1

Table 1 and Figure 1: Antiviral activity of ALG-001075 in HepG2.117 cells in comparison to the nucleoside inhibitor entecavir, the CAM II JNJ-320 and the CAM I RO7049389



Results 2 - In Vivo Antiviral Activity in the Mouse AAV-HBV Model

The AAV-HBV model was used to assess the efficacy of ALG-001075 in vivo. A dose-dependent reduction in plasma HBV-DNA levels was observed, with a maximum reduction of > 5 log_{10} IU/mL HBV DNA when ALG-001075 was dosed at 15 mg/kg BID for 56 days, with several animals reaching the limit of quantification. HBV-DNA levels returned to baseline levels within 2 weeks after the end of treatment (**Figure 2**). The reduction of plasma HBV-DNA concentrations in the 15 mg/kg ALG-001075 BID group exceeded the class II CAM comparator compound B dosed at 50 mg/kg BID. No or only minimal decreases in HBsAg or HBeAg were observed. All compounds were dosed by oral gavage.

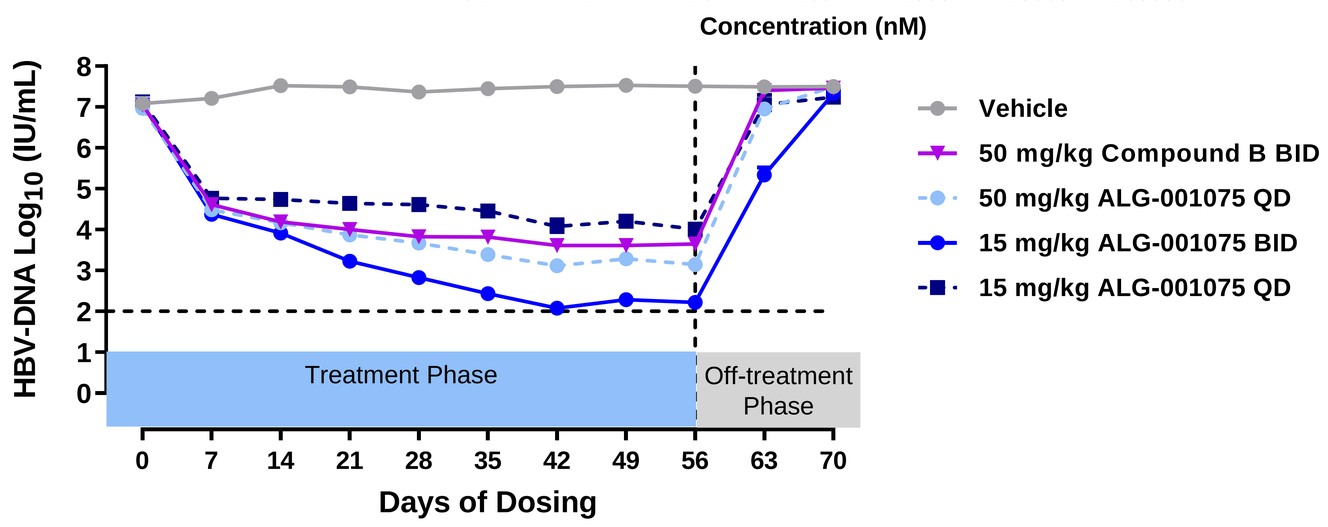


Figure 2: Significant in vivo efficacy was observed in the AAV-HBV mouse model when ALG-001075 was dosed PO at 15 mg/kg BID for 56 days as shown by a > 5 log_{10} IU/mL reduction in plasma HBV-DNA

Results 3 - In vitro Drug-Drug Interaction (DDI) Potential

- Neither ALG-000184 (IC_{50} > 100 µM) nor ALG 001075 (IC_{50} > 20 µM) inhibited CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 enzymes
- ALG-001075 is unlikely to cause time dependent inhibition of human CYP2C8, CYP2C9, or CYP3A4
- ALG-001075 has low induction potential for CYP1A2, CYP2B6, and CYP3A4
- ALG-000184 and ALG-001075 has low DDI-potential mediated by major transporters

Transporter		*ALG-000184*		*ALG-001075 [a]*	
		Substrate	*Inhibitor Unbound IC_{50} (µM)*	*Substrate*	*Inhibitor Unbound IC_{50} (µM)*
Efflux Transporters	BCRP	No or Poor	90.8	No or Poor	>50
	BSEP	Not conducted	>100	Not conducted	>30
	MATE1	Inconclusive [b]	>100	No	>50
	P-gp	No or Poor	>100	Yes	>50
Uptake Transporters	OAT1	Inconclusive [b]	10.8	No	>50
	OAT3	Inconclusive [b]	>100	No	11.8
	OATP1B1	Yes at 10 µM	50.0	No	>50
	OATP1B3	Yes at 10 µM	51.1	No	>50
	OCT1	Inconclusive [b]	>100	No	>50
	OCT2	Inconclusive [b]	>100	No	>50

[a] Highest inhibition concentration tested for ALG-001075 was 30 µM in BSEP assay and 50 µM for the other assays. [b] Inconclusive due to significant conversion of ALG-000184 to ALG-001075 in assay.

Table 2: ALG-000184 and ALG-001075 have a low risk for DDI mediated by major efflux and uptake transporters

Conclusions:

ALG-001075 is a Class II CAM with broad and potent antiviral activity as demonstrated in the cell-based HBV-DNA log-drop assay. In the AAV-HBV mouse efficacy study, ALG-001075 reduced plasma HBV-DNA levels by > 5 log_{10} IU/mL after 56 days of dosing.

ALG-001075 and its prodrug ALG-000184 exhibit a low risk of DDI mediated by cytochromes and major efflux and uptake transporters. Based on its excellent antiviral potency, favorable pharmacokinetic properties and low risk for DDI, ALG-000184 is currently advancing through Phase I clinical testing.

References: [1] Berke JM, et al. Antimicrob Agents Chemother 2017;61(8):e00560-17; Zhang X et al., ACS Infect Dis 2019;5(5):759–68

[2] Debing Y et al., AASLD 2019; Jekle A et al., AASLD 2020; Zhang Q et al., EASL 2020

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