The Potentially Best-in-class HBV ASO ALG-170675 Demonstrates a Favorable Preclinical Profile: Efficacy in an AAV-HBV Mouse Model, Pharmacokinetics and Safety in Mouse and Monkey

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BACKGROUND

ALG-170675 (ACT201) is a next generation HBV ASO with dual RNase H and human TLR8 agonist activities and is currently in phase 1 clinical development. In vitro, ALG-170675 showed less caspase 3/7 induction than bepirovirsen (Bepi or GSK-836) and similar RNase H and hTLR8 activities as Bepi. In vivo, ALG-170675 demonstrated better efficacy, liver exposure and liver to kidney ratio than Bepi when dosed at 40 mg/kg x 6 in AAV-HBV mice.[1] No liver toxicity was observed when ALG-170675 was dosed at 50 mg/kg x 7 in either uninfected or HBV-infected PXB mice with humanized livers.[2] Here, ALG-170675 was compared to Bepi head-to-head in repeat dosing of 40 mg/kg, 20 mg/kg and 10 mg/kg in AAV-HBV mouse model. A close analog of ALG-170675 was dosed in an AAV-HBV mouse model in combination with a close analog of ALG-000184 (HBV CAM-E). ALG-170675 combinations with the nucleos(t)ide analog (NA) entecavir (ETV), HBV siRNA ALG-125903 (parent drug of ALG-125755) and ALG-001075 (parent drug of ALG-000184) were also studied in vitro. Pharmacodynamics (PD), pharmaco-/toxicokinetics (PK/TK) and toxicology of ALG-170675 were evaluated in mouse and monkey.

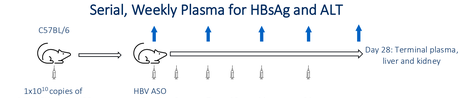
METHODS

HBV cell models, such as HepG2.2.15 and HepG2.117, were used for combination studies in vitro to assess reduction in HBsAg and HBV DNA, respectively. In vivo ALG 170675 dose response and combination studies were performed in the AAV-HBV mouse model. PK, PD and toxicity/TK evaluations in mouse and monkey were conducted at Wuxi AppTec.

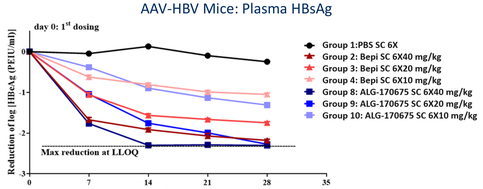
RESULTS

AAV-HBV Mouse Model: ALG-170675 Exhibited Dose Response Related Efficacy and Lower ALT Induction than Bepi

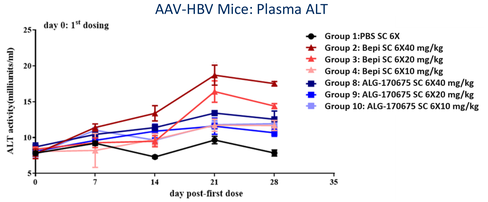
Serial, Weekly Plasma for HBsAg and ALT



AAV-HBV Mice: Plasma HBsAg



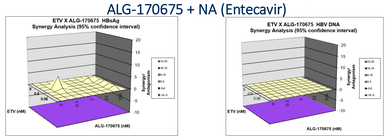
AAV-HBV Mice: Plasma ALT



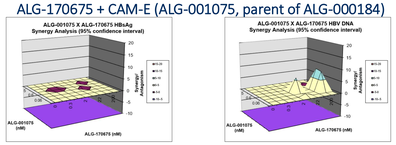
RESULTS

In Vitro Combinations on HBsAg and HBV DNA Reductions in HepG2.2.15 and HepG2.117 Cell Lines Respectively: ALG-170675 Showed Additive Effects When Combined with Other HBV Drugs

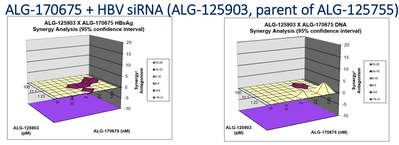
ALG-170675 + NA (Entecavir)



ALG-170675 + CAM-E (ALG-001075, parent of ALG-000184)



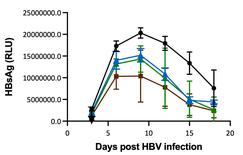
ALG-170675 + HBV siRNA (ALG-125903, parent of ALG-125755)



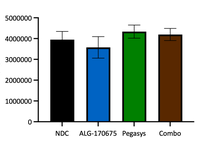
ASO	Compound Class			Synergy Volume		Synergistic/ Antagonistic Interaction	Cytotoxicity
	NA	CAM-E	siRNA	HBsAg (μM^3%)	HBV DNA (μM^3%)		
ALG-170675	ALG-000003 (entecavir)	–	–	15.2	0	Additive	No
	–	ALG-001075		-2.7	19.44	Additive	No
			ALG-125903	-17.99	-2.55	Additive	No

Emulate 3-D Human Liver Chips: ALG-170675 and Pegasys Combination Demonstrated an Additive Effect in Reducing HBsAg in the Supernatant

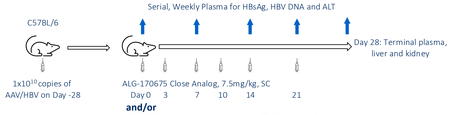
HBsAg in Supernatant



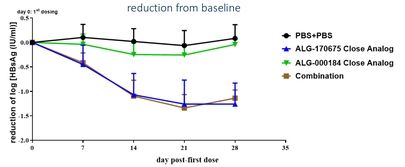
Cell Viability at End of Study



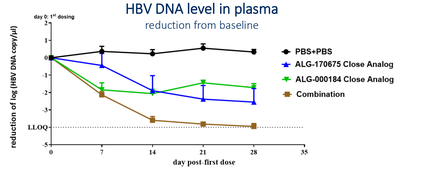
AAV-HBV Mouse Model: Close Analogs of ALG-170675 and ALG-000184 Combination Exhibited Additive Effects



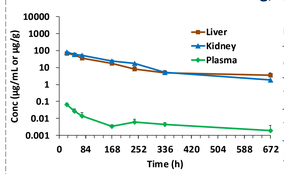
HBsAg level in plasma
reduction from baseline



HBV DNA level in plasma
reduction from baseline



Rapid Absorption and Distribution of ALG-170675 Following a Single SC Dose at 20 mg/kg in CD-1 Mice



PK parameters (N=3)	Plasma	Liver	Kidney
C_{max} (μg/mL or μg/g)	23.1	65.3	80.3
T_{max} (h)	0.500	24.0	24.0
$T_{1/2}$ (days)	11.4	6.8	5.0
$AUC_{0\text{-last}}$ (h·μg/mL or h·μg/g)	47.5	8610	11018

- Rapid absorption and distribution; long half-life in plasma, liver and kidney
- Low levels (0.2-0.7% of the parent molar AUC) of 3'- and 5'- N-1 metabolites observed in plasma, liver and kidney
- Total urinary excretion ($Fe_{0\text{-}24}$, % of dose) of the parent and two metabolites at 6.89% was low with parent as the major component

30 mg/kg/dose Identified as NOAELs in 1-Month/7-Dose Mouse and Monkey Dose Range-Finding Toxicology Studies

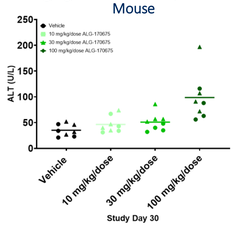


- Doses: 0 (vehicle), 10, 30, 100 mg/kg/dose to male and female CD-1 mice (n = 8/sex/group) and cynomolgus monkeys (n = 1/sex/group)
- ALG-170675 was well tolerated and plasma/tissue exposures increased with dose in both mice and monkeys up to 100 mg/kg/dose

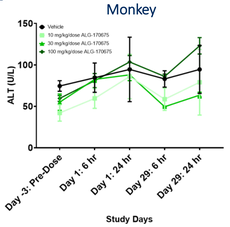
Dose Level (mg/kg/dose)	Mouse (Day 30)		Monkey (Day 29/30)			
	Liver (μg/g)	Kidney (μg/g)	Liver (μg/g)	Kidney (μg/g)	Plasma C_{max} (μg/mL)	Plasma $AUC_{0\text{-}24}$ (μg·h/mL)
10	87.8	144	428	1070	38.7	331
30	254	206	1130	1950	89.2	950
100	820	615	1940	6630	165	2550

- In mice, minimal to mild hepatocellular necrosis in females at ≥30 mg/kg/dose and in both sexes at 100 mg/kg/dose with ↑ALT/AST at 100 mg/kg/dose

Mouse

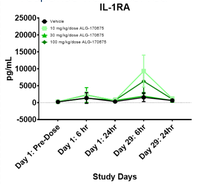


Monkey

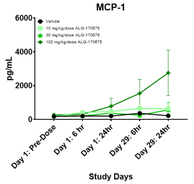


- Pharmacodynamic markers IL-1RA, MCP-1, and CRP were elevated in monkeys, but no dose-response was observed

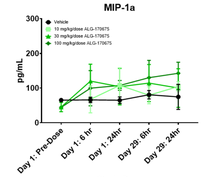
IL-1RA



MCP-1



MIP-1a



- In monkeys, the female at 100 mg/kg/dose had severely decreased lymphocytic cellularity in thymus with corresponding decrease in thymus weight and a macroscopically small thymus.
- Typical oligonucleotide related non-adverse findings of basophilic granules noted in liver, kidney and injection sites, reflecting oligonucleotide uptake in both mice and monkeys
- **NOAELs in both species were 30 mg/kg/dose and supported further development (Amoytop AASLD 2026 Publication # 4168).**

CONCLUSIONS

- **ALG-170675 demonstrated best-in-class potential: deeper HBsAg knockdown and less ALT induction than Bepi in an AAV-HBV mouse model**
- **ALG-170675 showed additive effects when combined with CAM-E, NA, siRNA and pegylated-IFN in vitro and an additive effect when combined with a CAM-E in vivo**
- **ALG-170675 was absorbed and distributed rapidly in mice; the half-life was long in plasma, liver and kidney**
- **NOAELs in both mouse and monkey were 30 mg/kg/dose and supported further development (Amoytop AASLD 2026 Publication # 4168)**
- **ALG-170675 (ACT201) has advanced to Phase 1 clinical studies.**

Financial Disclosures: Authors are or were the employees of Aligos Therapeutics Inc. or Amoytop Biotech. and may own stock of respective companies.

REFERENCES

1. Hong J. et al. Publication Number Fri-257, EASL May 7-10, 2025
2. Hong J. et al. Publication Number 1155, AASLD November 7-11, 2025

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