HBV ASO ALG-170674 Demonstrates Additive to Synergistic Antiviral Activities when Combined with Other anti-HBV Modalities in Preclinical Studies

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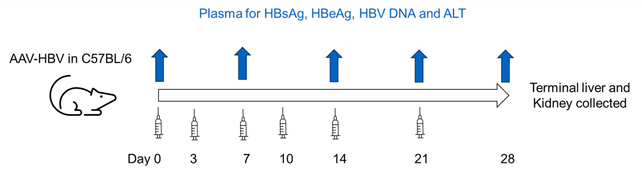
Background and Aims

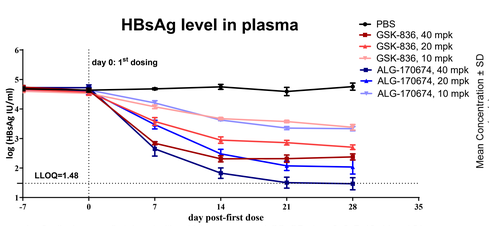
Chronic hepatitis B (CHB) patients can achieve a modest rate of functional cure after monotherapy with antisense oligonucleotides (ASO) e.g., bepirovirsen (GSK-836) and AHB-137. To enhance the rate of functional cure, it will be important to combine HBV ASOs with other modalities of HBV drugs. ALG-170674, an analog of the HBV ASO clinical development candidate ALG-170675, is a next generation HBV ASO that showed superior in vivo RNase H-mediated activity, as well as PK, compared to GSK-836 in an AAV-HBV mouse model. ALG-170674 also exhibited improved binding over GSK-836 to the human TLR8 protein. ALG-001075 is the parent of the investigational CAM-E prodrug, pevifoscorvir sodium (pevy, ALG-000184). In a 96-week Phase I study in CHB patients, ALG-000184 demonstrated the ability to dramatically reduce HBV viral load in all patients, as well as HBsAg in HBeAg+ patients. In this study, we demonstrate the antiviral effects of ALG-170674 in monotherapy and in combination with ALG-001075 or its analog in HBV cell and animal models. The effects of ALG-170674 in combination with other modalities such as nucleos(t)ide analogs (NAs), HBV siRNA and pegylated interferon (IFN) were also studied.

Methods

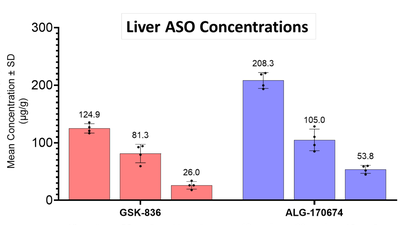
- HBV ASOs ALG-170674 and GSK-836, as well as ALG-125903 (unconjugated version of Aligos clinical HBV siRNA ALG-125755), were synthesized at Aligos Therapeutics.
- CAM-E ALG-001075 and its analog ALG-000111, as well as ALG-000286 (prodrug of ALG-000111, analog of ALG-000184), were synthesized at Aligos Therapeutics.
- Other commercially available CHB drugs - entecavir (ETV) and Pegasys, were purchased.
- AAV-HBV mouse model was used to measure the in vivo RNase H-mediated activities of ALG-170674 and GSK-836. Liver and Kidney ASO levels were analyzed by LCMS.
- Human TLR8 knock-in mouse model was used to analyze the immunoactivities of ALG-170674 and GSK-836 in vivo.
- HepG2.2.15 cell line was used to analyze combination effects towards HBsAg by ALG-170674 (with transfection) and other anti-HBV agents.
- HepG2.117 inducible cell line was used to analyze combination effects towards secreted HBV DNA by ALG-170674 (with transfection) and other anti-HBV agents.
- Emulate 3-D liver chips were used to analyze the combination effects on HBsAg by ALG-170674 (by free-uptake, without transfection) and other anti-HBV agents.
- AAV-HBV mouse model was used to analyze the combination effects on mouse plasma HBsAg and HBV DNA following administration of ALG-170674 (subcutaneous injections) and CAM-E pro-drug ALG-000286 (oral gavage).

AAV-HBV Mouse Model: ALG-170674 Showed Higher In Vivo Efficacy and Higher Liver Exposures Compared with GSK-836; No ALT Elevations Noted

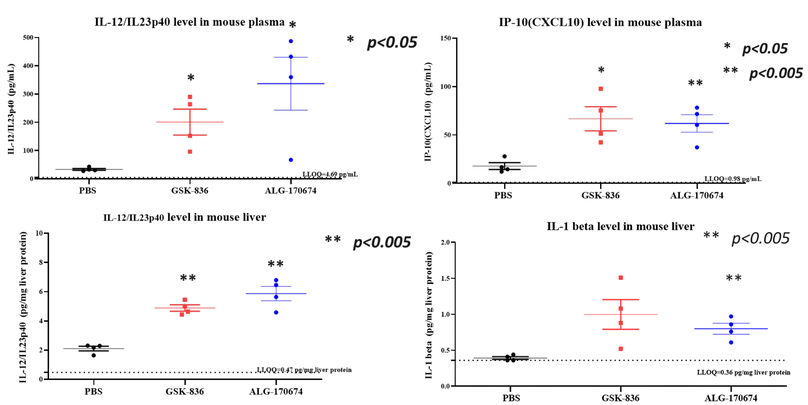




day 0: all mice were first dosed with vehicle or compoundsSC, QD, days 0, 3, 7, 10, 14 and 21

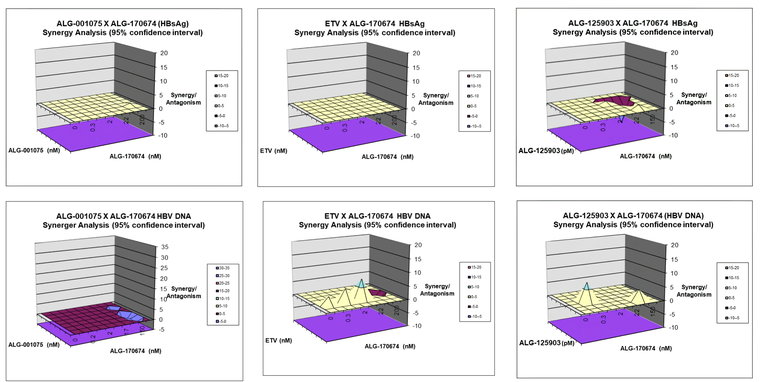


Human TLR8 Knock-in Mouse Model: ALG-170674 Demonstrated Similar Cytokine / Chemokine Induction as GSK-836



ALG-170674 with Transfection Showed Additive Effects when Combined with Other CHB Compounds in HepG2.2.15 and HepG2.117 Cell Lines

MacSynergy II Synergy/Antagonism Volumes Description @ 95% Confidence	
Volume (µM2%)	Volume Description
<25	Insignificant synergism (+) / Insignificant antagonism (-): additivity
25-50	Minor synergism (+) / Minor antagonism (-)
50-100	Significant synergism (+) / Significant antagonism (-): maybe important in vivo
>100	Strong synergism (+) / Strong antagonism (-): probably important in vivo
>1000	Probable errors



	ALG-170674 + ALG-001075 (HBV ASO + CAM-E)	ALG-170674 + ETV (HBV ASO + NA)	ALG-170674 + ALG-125903 (HBV ASO + HBV siRNA)
HBsAg Combo Effects (Volume µM2%)	Additive (+ 0.79)	Additive (0)	Additive (- 18.85)
HBV DNA Combo Effects (Volume µM2%)	Additive (- 16.25)	Additive (+ 18.3)	Additive (+ 9.94)

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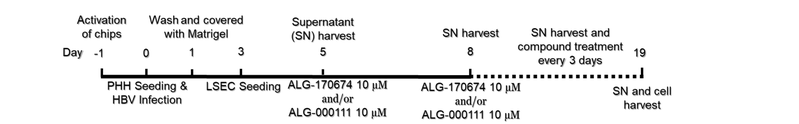
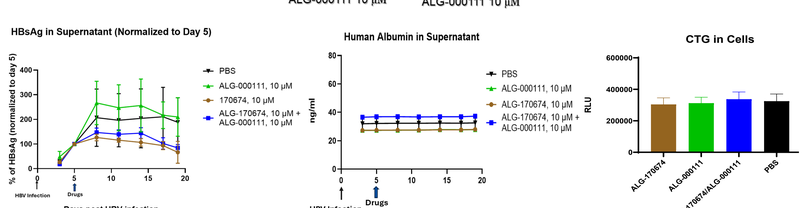
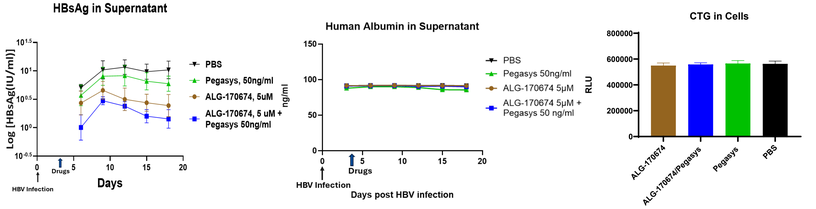
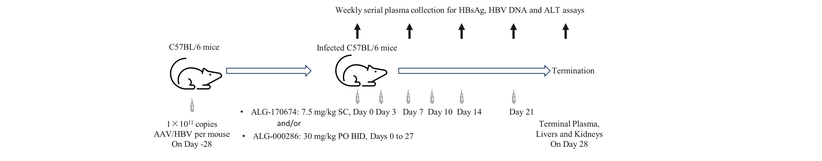
HBV ASO ALG-170674 through Free Uptake Exhibited Additive to Synergistic Effects when Combined with Other CHB Compounds in Emulate 3-D Liver Chips

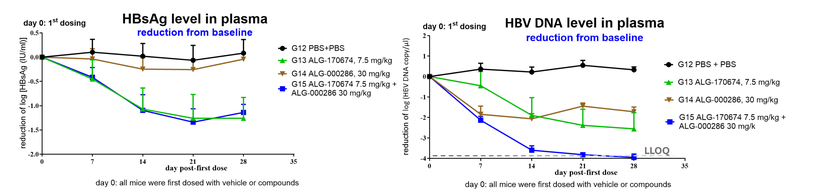






AAV-HBV Mouse Model: ALG-170674 Showed Additive to Synergistic Effects When Combined with the CAM-E Prodrug ALG-000286





- **ALG-170674 is a close analog of the Aligos HBV ASO development candidate ALG-170675. ALG-170674 showed improved liver PK / HBsAg reductions over GSK-836 in the AAV-HBV mouse model.**
- **ALG-170674 showed additive to synergistic effects in vitro and in vivo when combined with pevifoscorvir sodium or its close analog. Combinations with other anti-HBV modalities such as pegylated interferon, ETV and HBV siRNA also demonstrated additive to synergistic effects.**

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