FRONTIERS IN DRUG DEVELOPMENT FOR HEPATOLOGY
HEP-DART 2025
HILTON HAWAIIAN VILLAGE • HONOLULU, HAWAII
7-11 DECEMBER 2025

POSTER #1

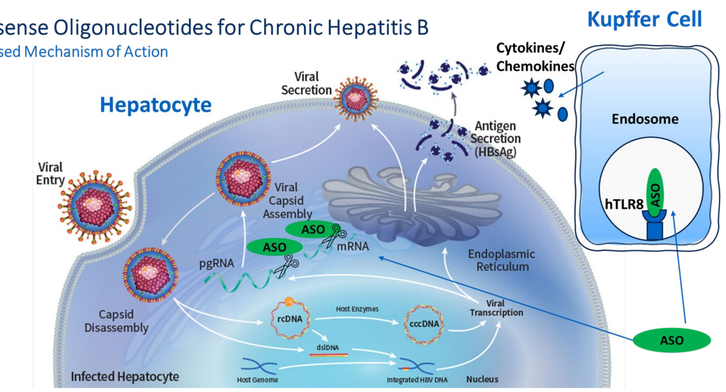
EXPLORATIONS TOWARDS THE SELECTION OF A POTENTIAL BEST-IN-CLASS HBV ASO

Jin Hong[1], Vivek K. Rajwanshi[1], Dinah Misner[1], Jimmy Lu[3], Kusum Gupta[1], Antitsa Stoycheva[1], Dana Cho[1], John Cortez[1], Min Luo[1], Hyunsoon Kang[1], Kellan Passow[1], Jacquelyn Sousa[1], Shane Daguison[1], Ji Eun Song[1], Lillian Adame[1], Cheng Liu[1], Sarah Stevens[1], Aneerban Bhattacharya[1], Rostom Ahmed-Belkacem[2], Susan Luong[1], Lawrence M. Blatt[1], Li Sun[3], David B. Smith[1], Leonid N. Beigelman[2] and Julian A. Symons[1]

[1]Current or [2]Former employees, Aligos Therapeutics Inc., 1 Corporate Drive, South San Francisco, CA 94080, USA
[3]Amoytop Biotech Co., No. 330 Wengjiao Road, Haicang, Xiamen, Fujian, P.R. China

BACKGROUNDS

Achieving functional cure in chronic hepatitis B will likely require direct antiviral and immunomodulatory drugs. Clinical stage HBV ASOs bepirovirsen (GSK-836)[1,2] and AHB-137[3] demonstrate dual RNase H-mediated direct antiviral and TLR8 agonist immunomodulatory activities. GSK-836 in monotherapy achieved a moderate functional cure rate of ~10% in a phase 2b trial, superior to other modalities (such as siRNA) but not optimal. Our aim is to develop a best-in-class HBV ASO with an improved overall therapeutic index over other clinical stage HBV ASOs.

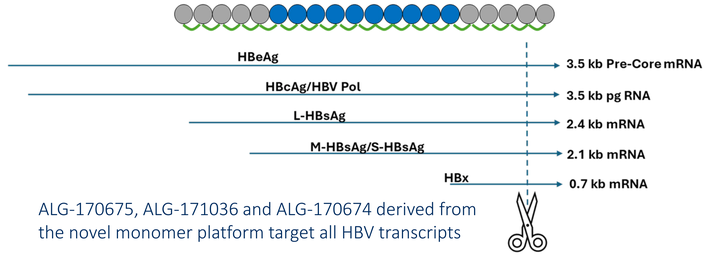


METHODS

RNase H-mediated activity was determined with an HBsAg ELISA in HepG2.2.15 cells and evaluated in vivo in AAV-HBV mice. To demonstrate ASO hTLR8 activity in vitro, HEK-Blue hTLR8 cell line was used. For in vivo testing, hTLR8 knock-in mice were dosed with ASO subcutaneously and mouse cytokine induction was measured. Toxicity derived from ASO off-target effects was determined in a HepG2 Caspase3/7 assay and by using an ATP assay in InSphero 3-D liver microtissues. A PXB mouse model with humanized livers was used to assess the potential hepatotoxic effect of the lead ASO constructs.

RESULTS

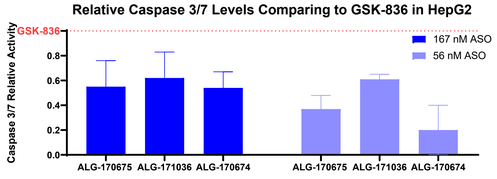
ASO PLATFORM WITH NOVEL MONOMER(S)



ALG-170675, ALG-171036 and ALG-170674 derived from the novel monomer platform target all HBV transcripts

NOVEL CHEMISTRIES RESULTED IN LOWER T_M, LESS OFF-TARGET ACTIVITY

ASO ID	T_m for Duplex with RNA Target (°C)	HepG2.2.15 HBsAg Knock-Down EC_{50} (nM)	HepG2.2.15 CTG CC_{50} (nM)
GSK-836	58.1	6.5 ± 2.8	>167
ALG-170675	50.2	8.8 ± 1.8	>167
ALG-171036	53.5	2.5 ± 0.2	>167
ALG-170674	48.9	11.6 ± 3.0	>167

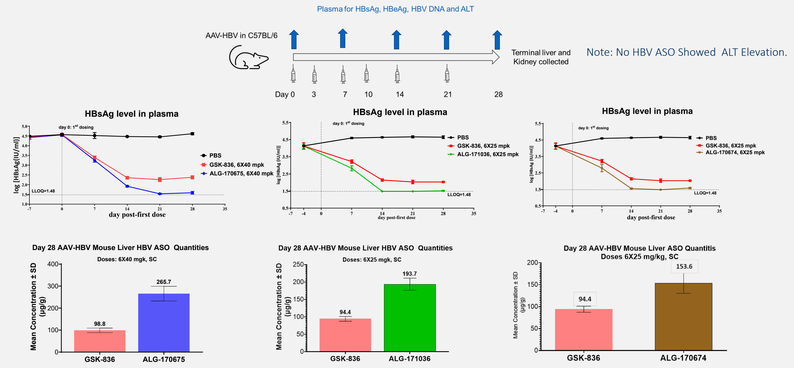


RESULTS

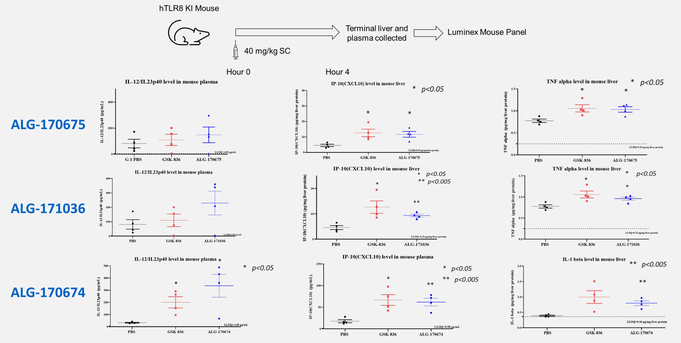
ALIGOS ASO LEADS SHOWED MODERATE HTLR8 AND REDUCED HTLR9 AGONIST ACTIVITIES

ALG#	hTLR7 Emax Fold vs. PBS	hTLR8 Emax Fold vs. PBS	hTLR9 Emax Fold vs. PBS	mTLR8 Emax Fold vs. PBS	Null Emax Fold vs. PBS
GSK-836	1.07	1.89	1.29	1.06	1.12
ALG-170675	1.03	1.87	1.18	1.06	1.07
ALG-171036	1.07	2.24	1.22	1.02	1.11
ALG-170674	1.07	2.17	1.15	1.13	1.07
R848 Ctrl. (TLR7/8 Agonist)	3.71	6.15		1.04	1.01
R837 Ctrl. (TLR7 Agonist)	1.66				1.01
GS9688 Ctrl. (TLR8 Agonist)		7.30		1.00	1.03
ODN2006 Ctrl. (TLR9 Agonist)			2.33		1.03

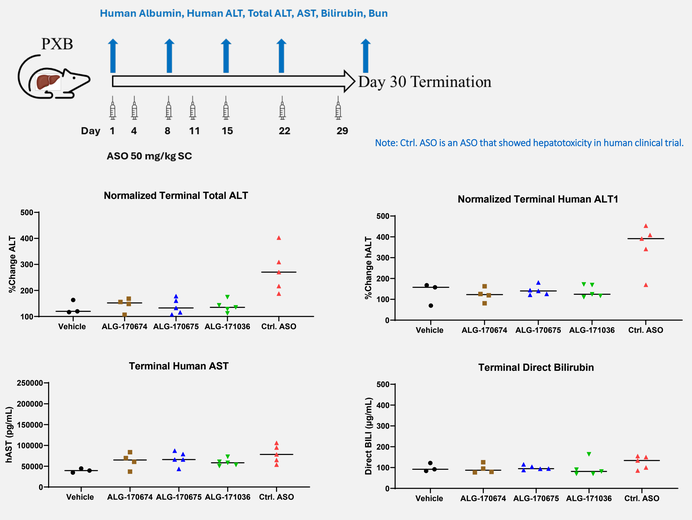
LEAD ASOS SHOWED IMPROVED RNASE H MEDIATED IN VIVO ACTIVITY OVER GSK-836 IN AAV-HBV MICE WITH IMPROVED LIVER EXPOSURE



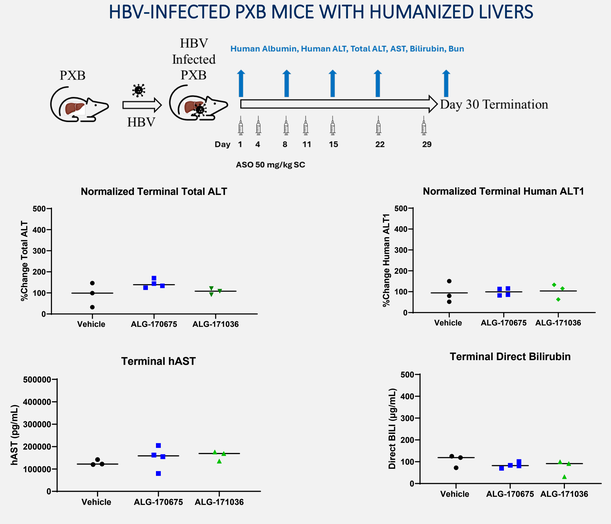
LEAD ASOS SHOWED SIMILAR CYTOKINE INDUCTION PROFILES TO GSK-836 IN HTLR8 KNOCK-IN MICE



ALG-170675, ALG-171036 AND ALG-170674 EXHIBITED NO LIVER TOXICITY IN UNINFECTED PXB MICE WITH HUMANIZED LIVERS



ALG-170675 AND ALG-171036 DEMONSTRATED NO LIVER TOXICITY IN HBV-INFECTED PXB MICE WITH HUMANIZED LIVERS



CONCLUSIONS

- **ALG-170675 ALG-171036 and ALG-170674 are optimized HBV ASO leads that emerged as the top three candidates after PXB mouse studies**
- **All 3 ASOs showed lower Tm and less in vitro cytotoxicity than GSK-836**
- **Improved in vivo efficacy and liver exposure in AAV-HBV mice was observed when compared to GSK-836 with all 3 ASO leads**
- **Similar immunomodulatory profiles as GSK-836 were observed in vitro and in vivo with 3 ASOs**
- **No hepatotoxicity in uninfected or HBV-infected PXB mice with humanized livers was observed with 3 ASOs**
- **Further investigations to advance selected HBV ASOs into clinical development are currently on-going**

REFERENCES
1. Yuen, M-F. et al. N. Engl. J. Med 387;21 November 24, 2022
2. You, S. et al. EASL 2022 Poster No. SAT439
3. Ding, Y. et al. AASLD 2024, Late Breaking Abstract Parallel Session 2

ACKNOWLEDGEMENTS

We thank leadership and scientific teams of Aligos and Amoytop for working closely together to achieve all the milestones in this project. Company employees may own stock or stock options in their companies.

CONTACT INFORMATION

Jin Hong, Ph.D.
jhong@aligos.com