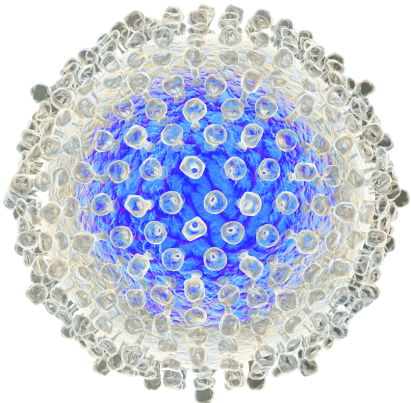
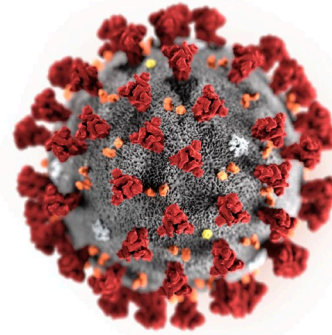




Preclinical Profile of ALG-125755, a GalNAc-siRNA Targeting HBV

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Except where otherwise indicated, the information contained in this presentation speaks as of the date hereof or as of the date at which such information is expressed to be stated, as applicable, and such information may express preliminary estimated, unaudited results which shall be subject to audit or other year-end adjustments and such audited or adjusted results may materially differ from those contained in this presentation.

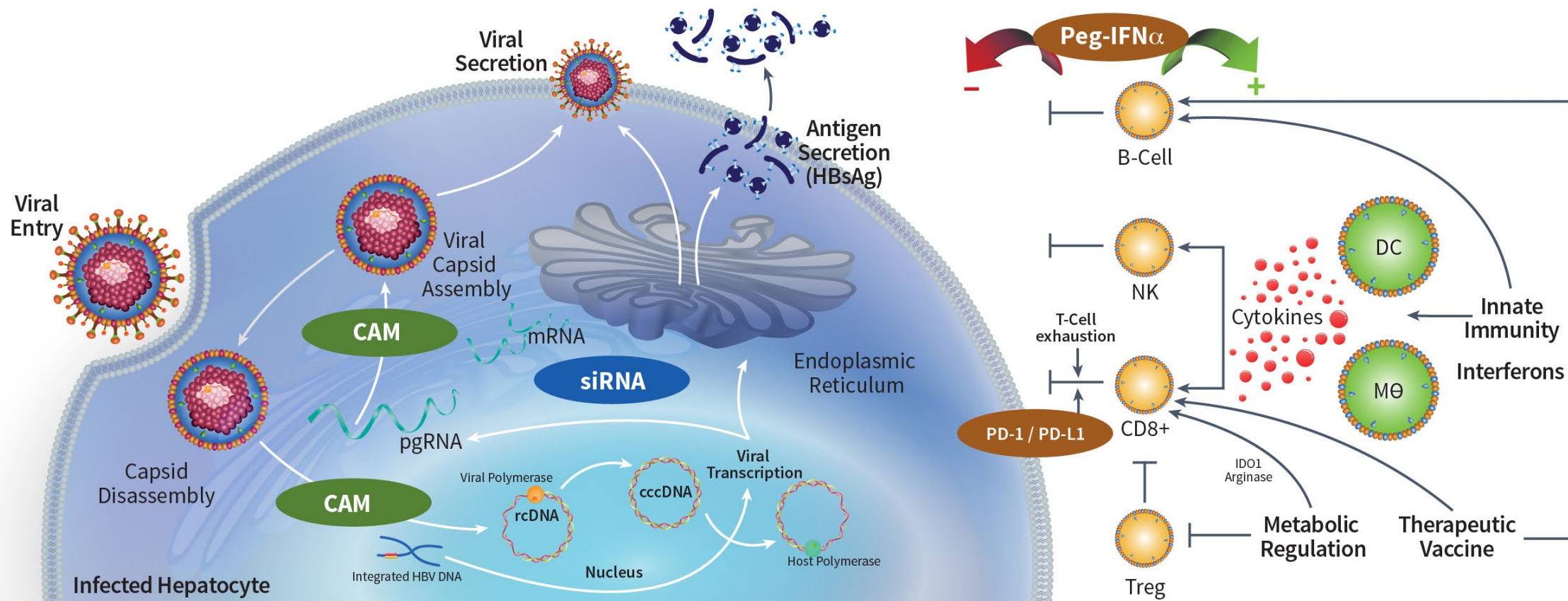
This presentation concerns drug candidates, some of which are undergoing nonclinical studies and others of which are under clinical investigation, and all of which have not yet been approved for marketing by the U.S. Food and Drug Administration. These drug candidates are currently limited by federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

Therapeutic Approaches to CHB Functional Cure

Inhibit Viral Replication

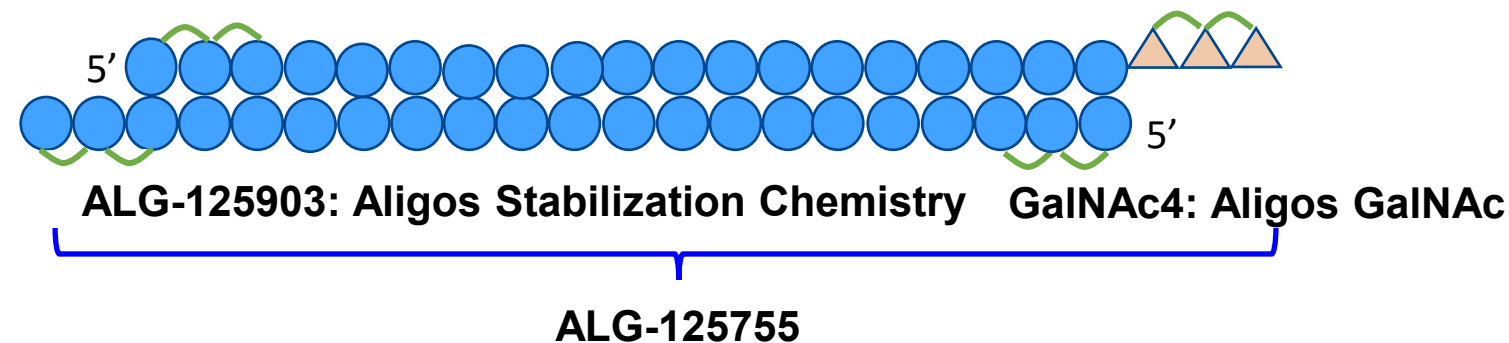
Lower Antigen Burden

Boost Immune Response



Aligos is developing CAM-E ALG-000184, siRNA ALG-125755 and liver targeting PD-L1 inhibitor

ALG-125755 Structure and Target Sequence



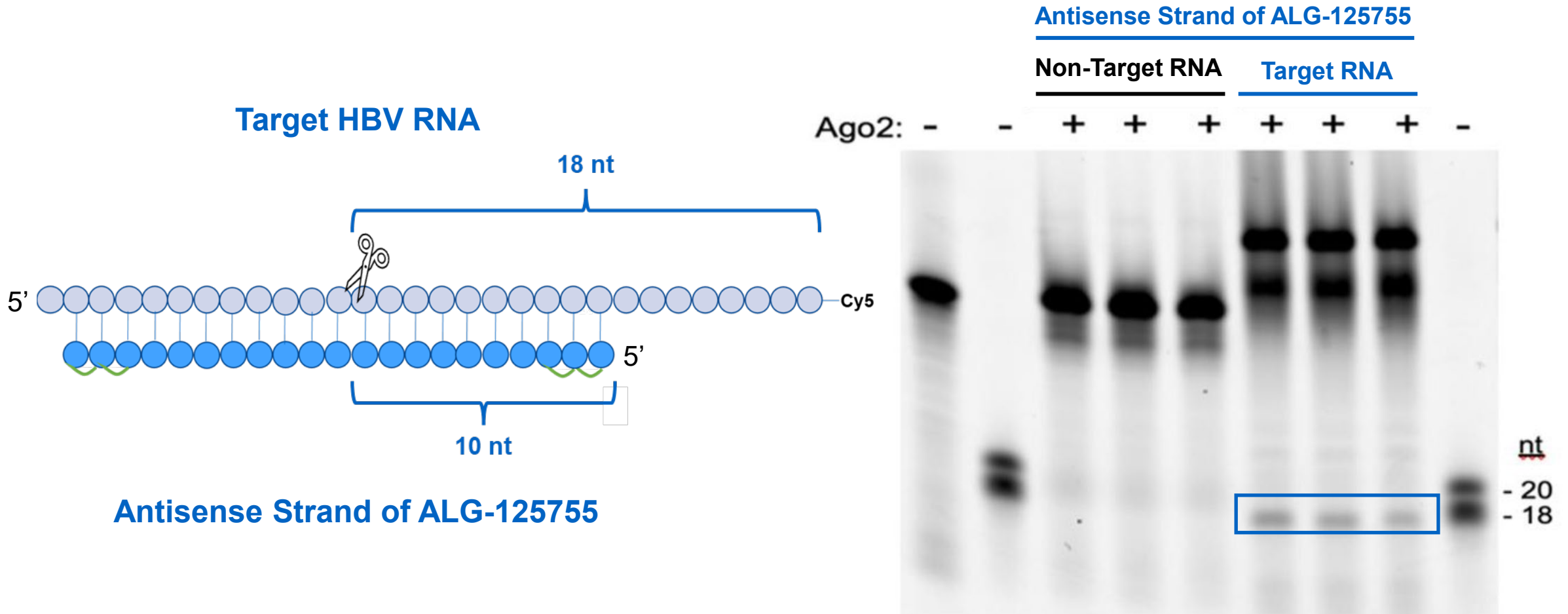
Homology to >9700 HBV Clinical Isolates

GalNAc siRNA	Gt A	Gt B	Gt C	Gt D	Gt E	Gt F	Gt G	Gt H	Gt I	Gt J
ALG-125755	100%	100%	100%	100%	100%	99%	100%	100%	100%	100%

Homology: 0 mismatch (95%) + 1 mismatch (5%)

ALG-125755 targets a very conserved HBV site and utilizes proprietary stabilization chemistries

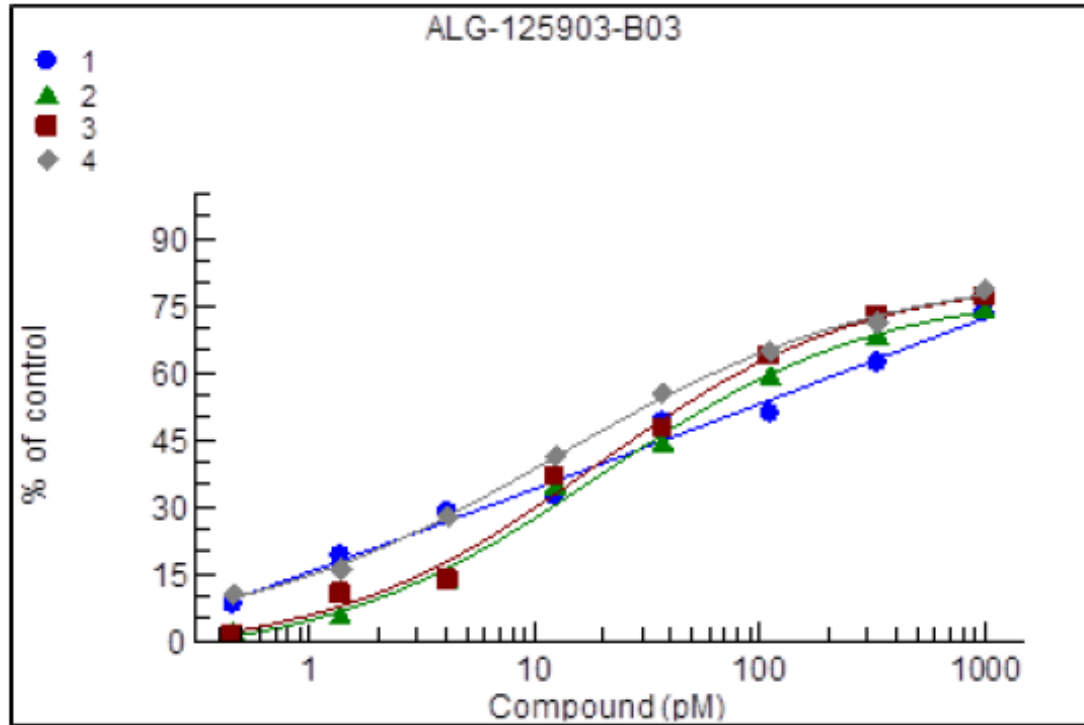
The Antisense Strand of ALG-125755 Demonstrates Activity in an Ago-2 Biochemical Assay



Ago-2 with antisense strand of ALG-125755 cleaves complementary HBV RNA at expected location

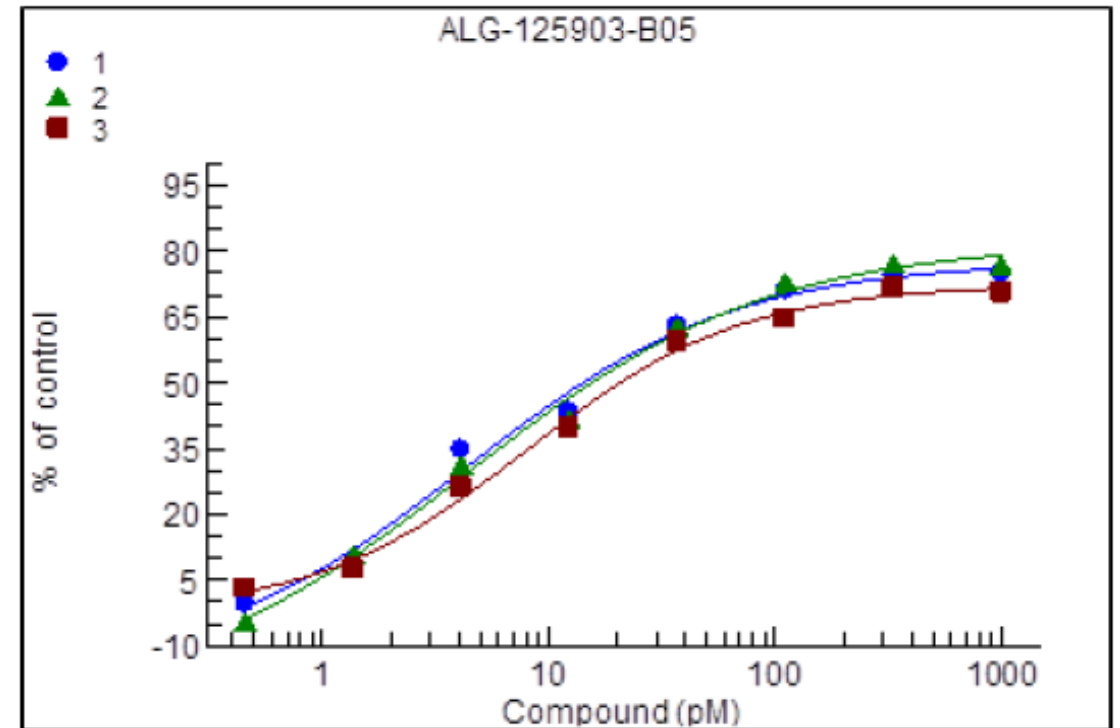
In Vitro Activity of ALG-125903: The Unconjugated Form of ALG-125755

HepG2.2.15



$EC_{50} = 17.48 \text{ pM}$; $CC_{50} > 1000 \text{ pM}$

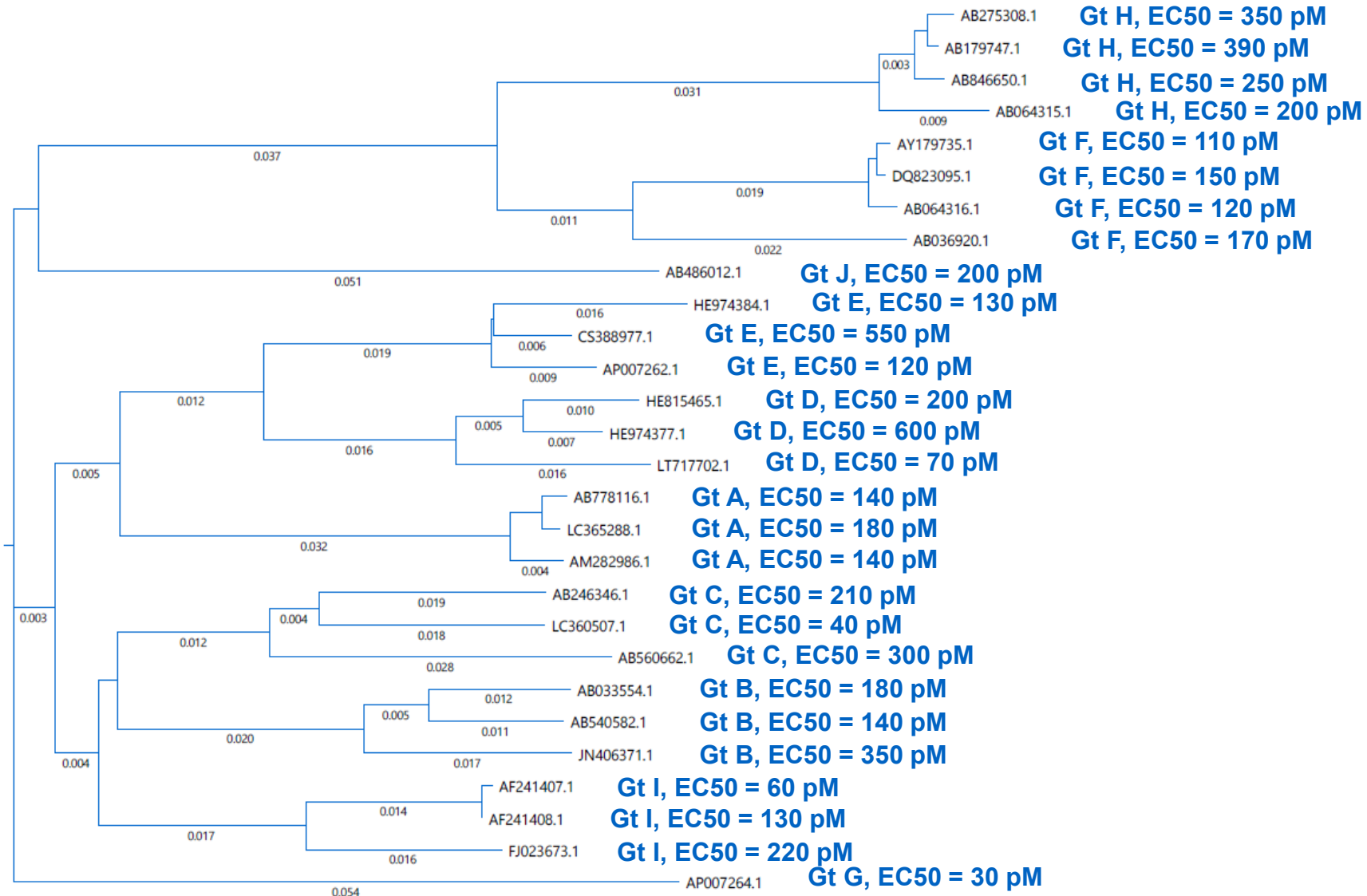
HBV Infected Primary Human Hepatocytes



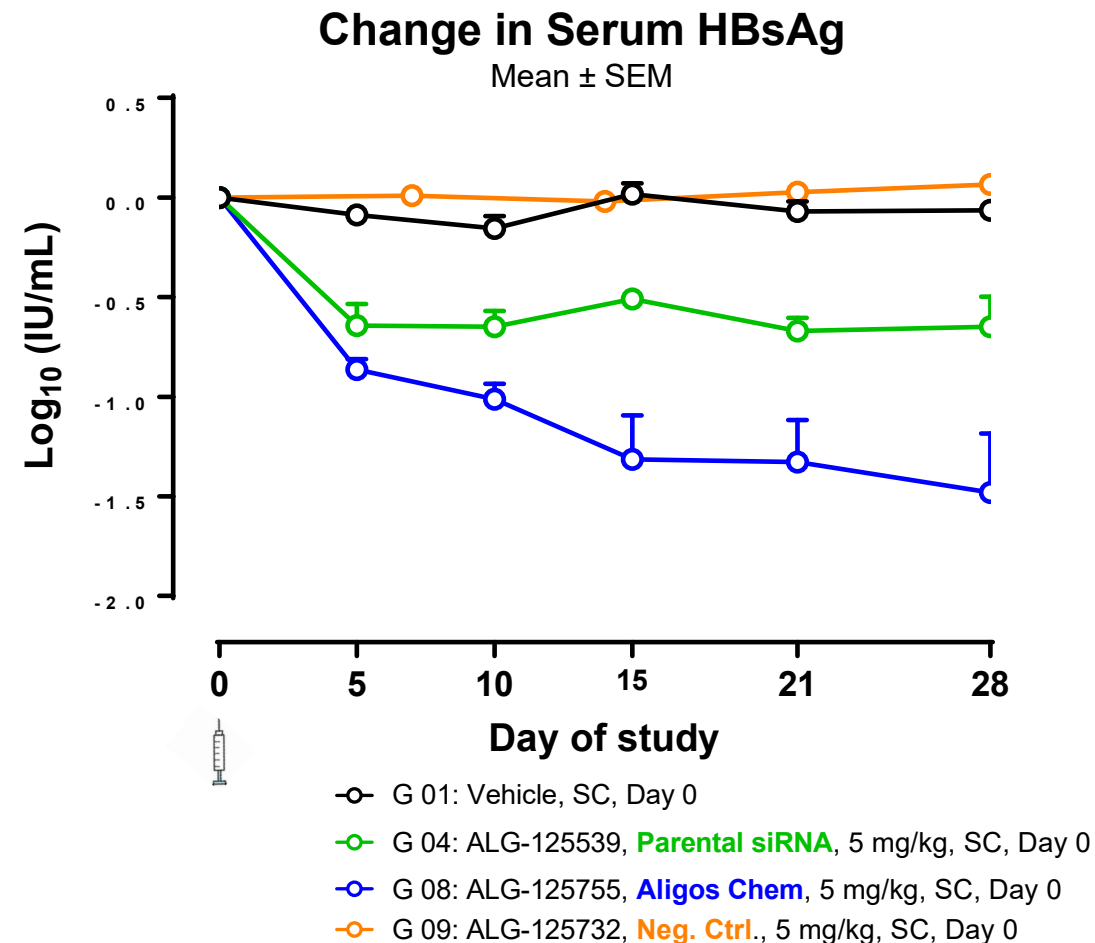
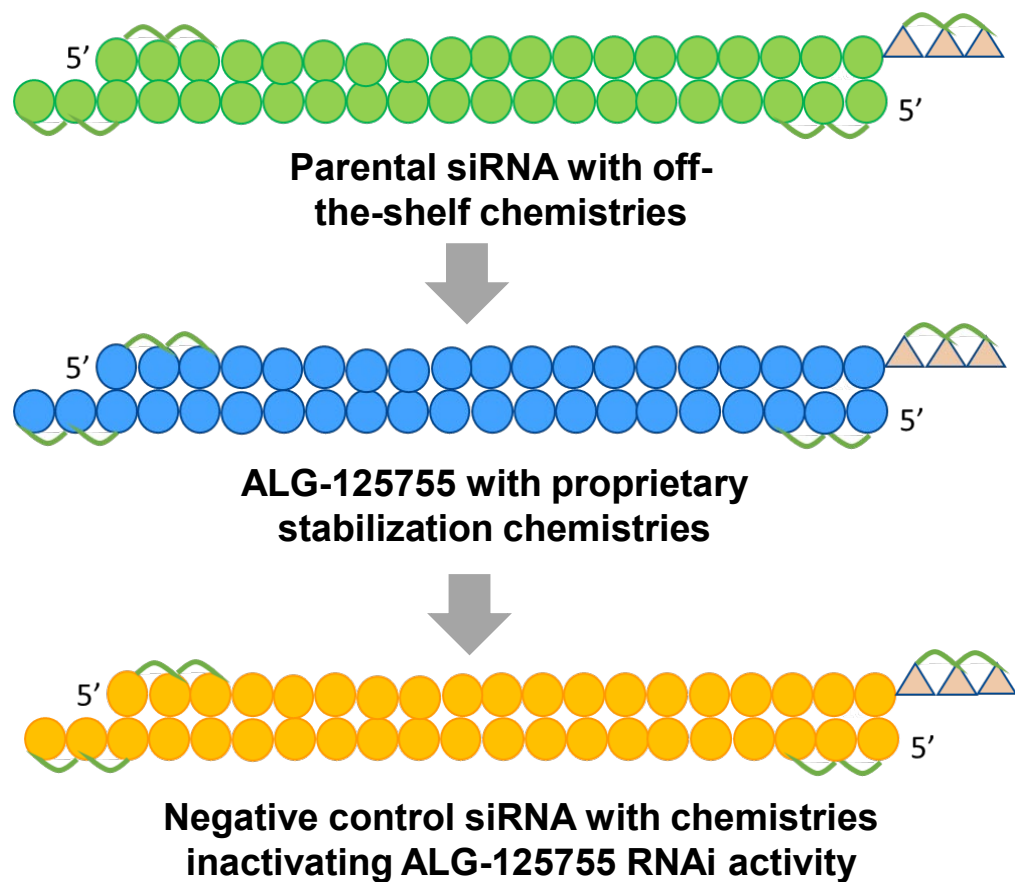
$EC_{50} = 5.58 \text{ pM}$; $CC_{50} > 1000 \text{ pM}$

Unconjugated version of ALG-125755 showed pM EC_{50} values in HBV cell models

ALG-125755 Demonstrated Potent Antiviral Activities vs. HBV Clinical Isolates



ALG-125755 In Vivo Activity in the AAV-HBV Mouse Model



ALG-125755 incorporating proprietary chemistries showed significant improvement over parental siRNA

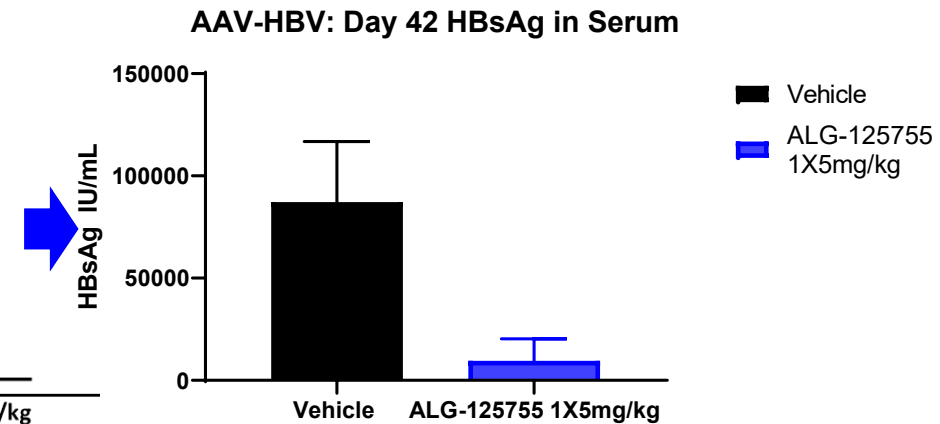
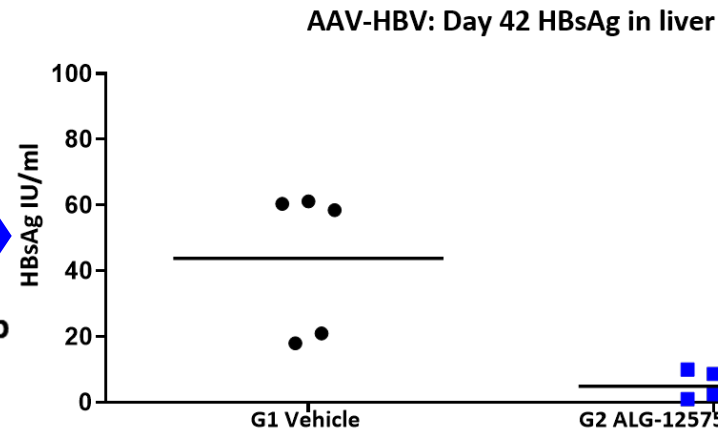
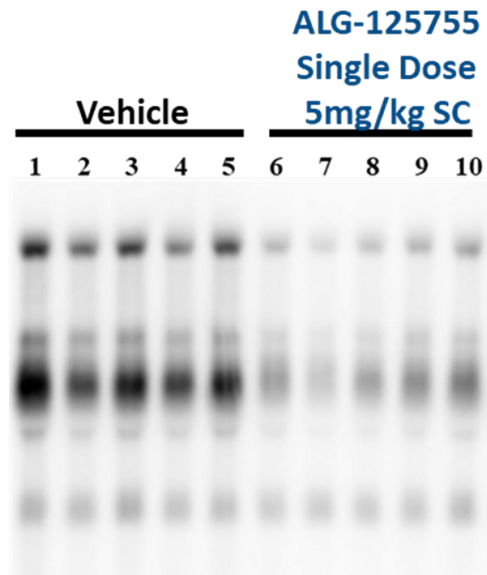
ALG-125755: In Vivo MOA Analysis at the End of Study

AAV HBV: 42 days post single dose of 5 mg/kg

Liver HBV RNA by Northern

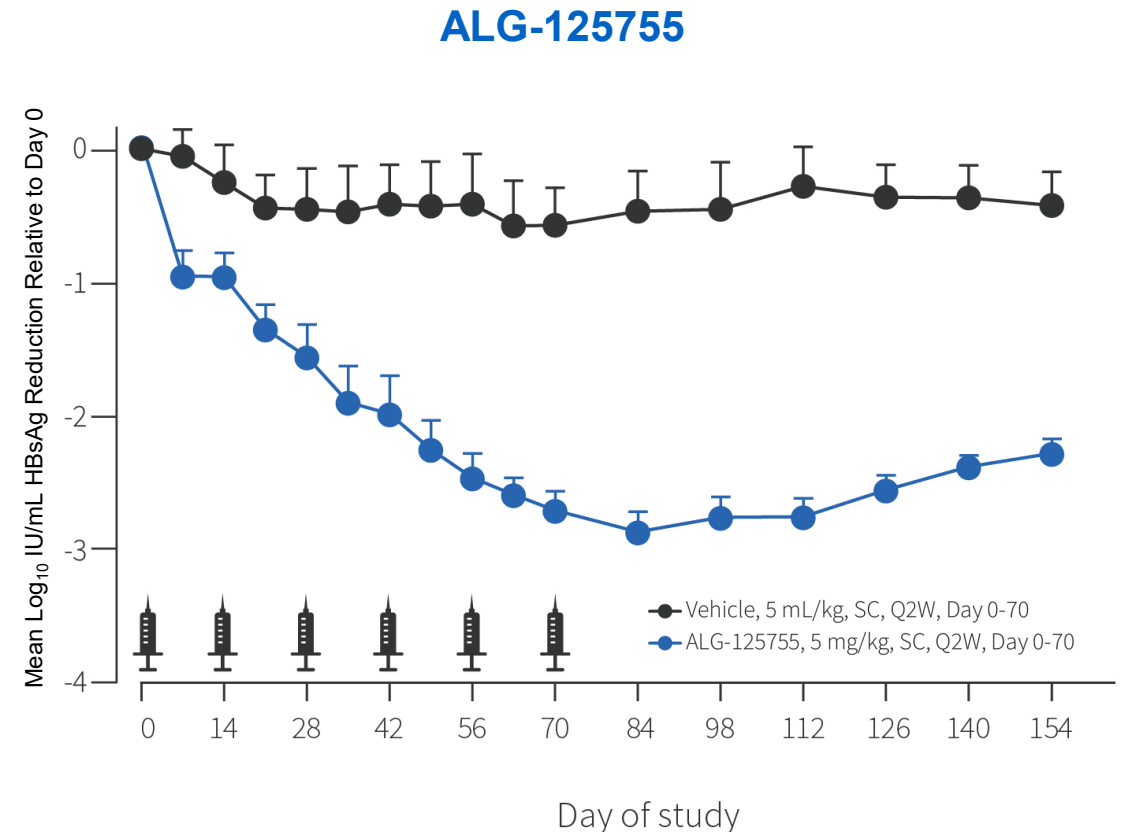
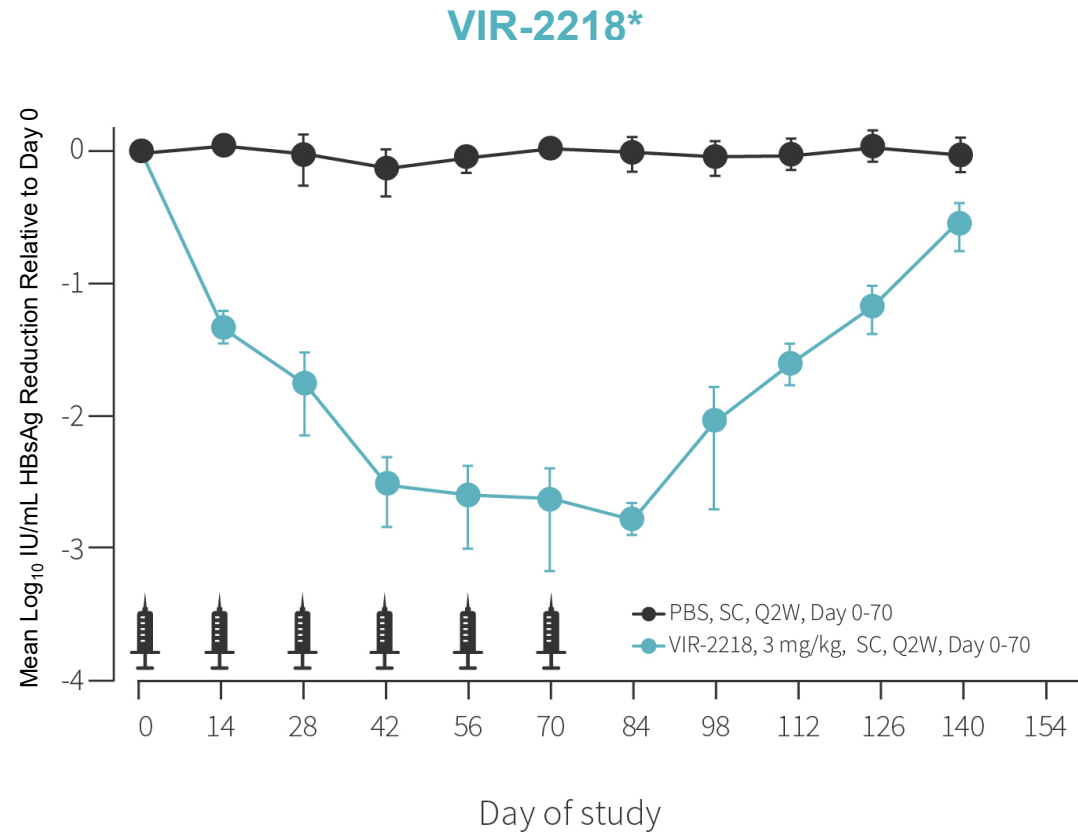
Liver HBsAg by ELISA

Serum HBsAg by ELISA



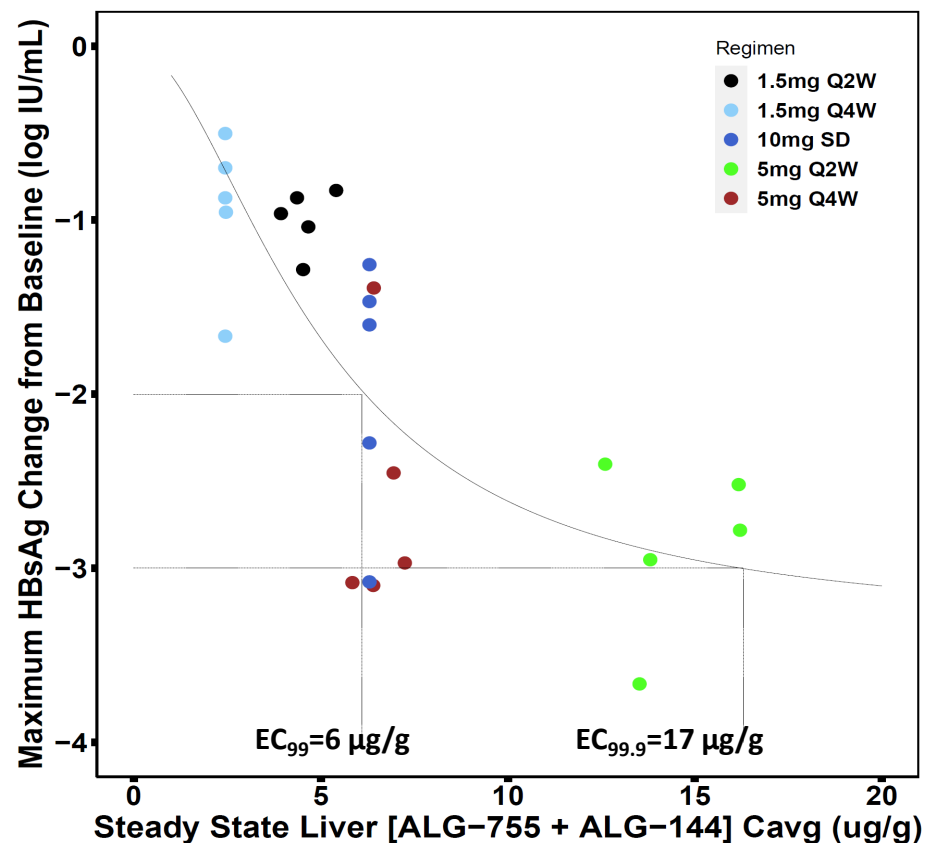
ALG-125755 MOA: reduction of serum HBsAg was due to cleavage of HBV RNA in liver through RNAi

ALG-125755: Repeat Dosing in the AAV-HBV Mouse Model vs. VIR-2218



ALG-125755 demonstrates a more sustained reduction in HBsAg vs. competitor siRNAs

ALG-125755: PK-PD Correlation in Mouse

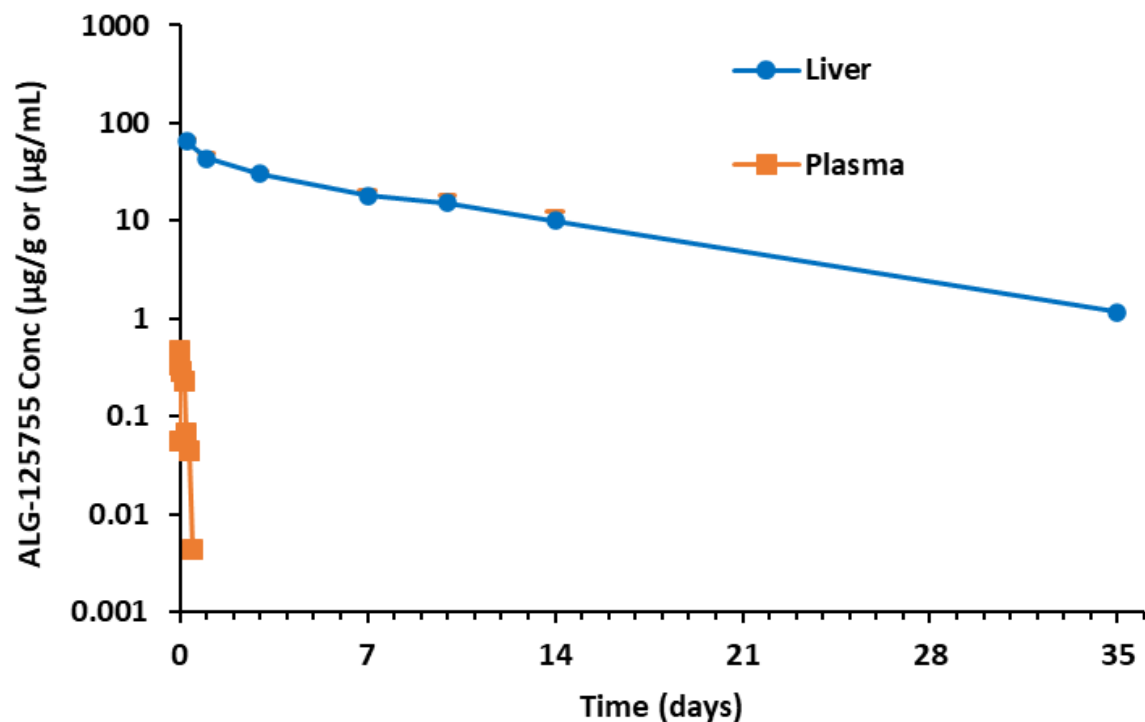


- For siRNA, C_{avg} appears to be more relevant PK parameter for efficacious target
- Only maximum HBsAg change from baseline was considered; sustained PD durability was not taken into consideration for the mouse PK/PD analysis
- ALG-126144 is 3' N-1 active metabolite

Target efficacious liver exposure = 6 $\mu\text{g/g}$

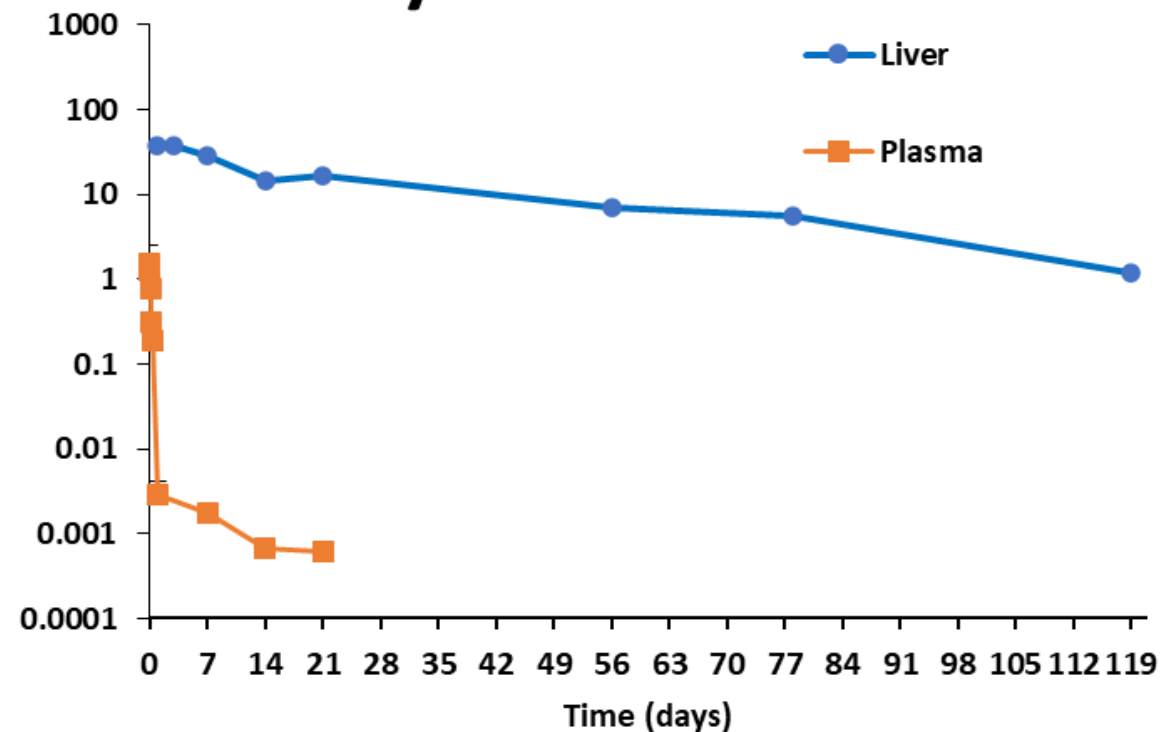
ALG-125755: Single SC Dose PK at 5 mg/kg in Rat and Monkey

Rat



Rat liver C_{max} 64.8 µg/g and $T_{1/2}$ 6.8 days

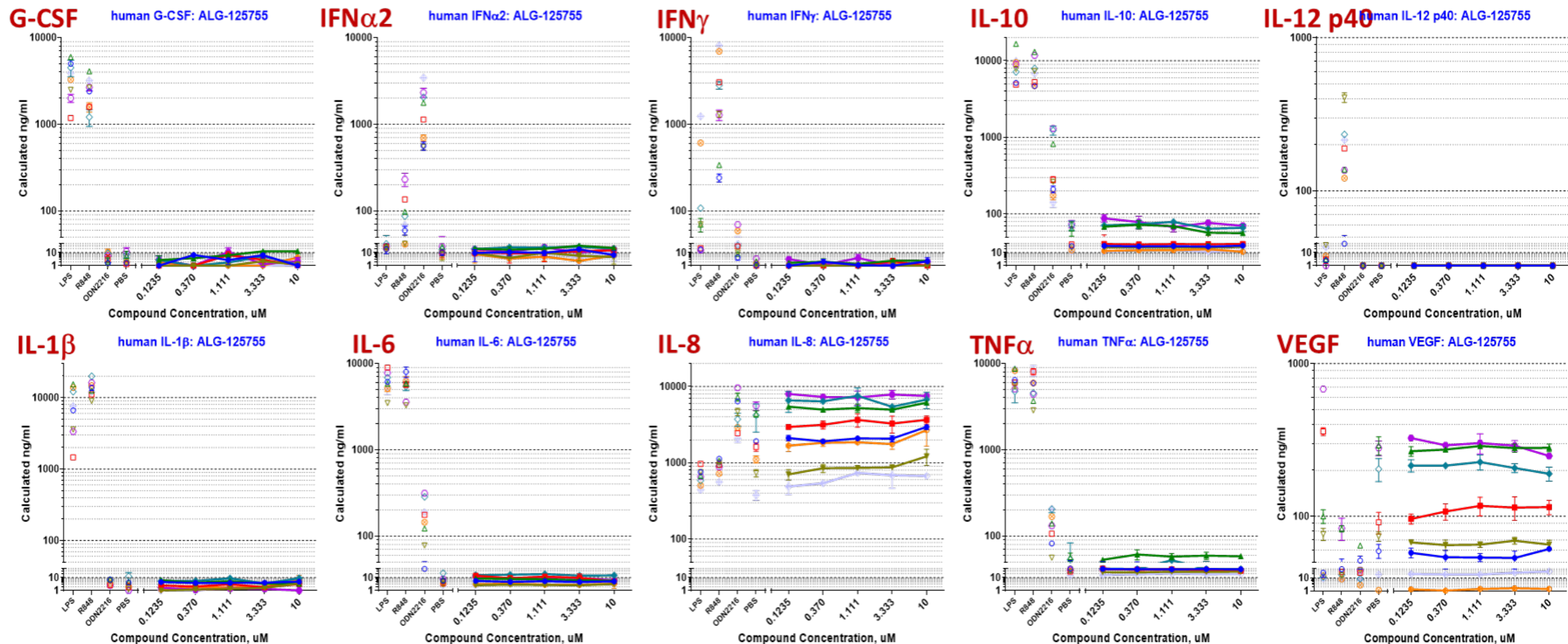
Monkey



Monkey liver C_{max} 38.4 µg/g and $T_{1/2}$ 26.4 days

ALG-125755 single SC injection in rat and monkey: high liver exposure and long liver half life

ALG-125755 Activity in a Human PBMC Assay



ALG-125755 showed no immune activation in cytokine release assays performed in PBMC from 8 donors

ALG-125755 In Vitro Off Target Profile

- Experimentally investigated potential off targets identified by bioinformatics

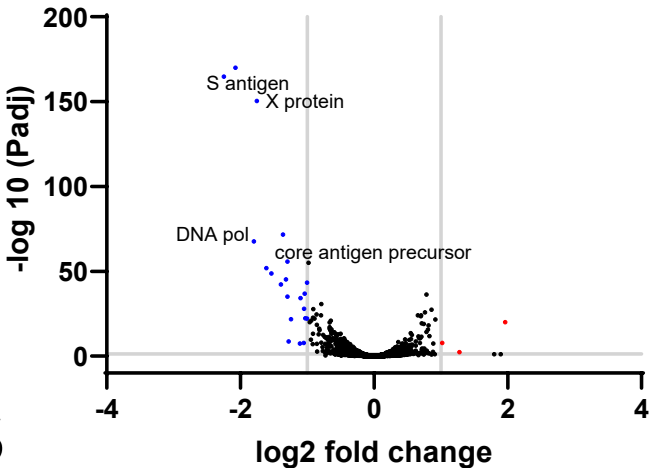
Human mRNA	0 MM	1 MM	2 MM	3 MM	4 MM
ALG-125755 hits	0	0	0	0	7

Gene	Primer No.	HepG2.2.15	HepG2.2.15
		25 pM (96 hour)	250 pM (96 hour)
Gene 1	1	0.53±0.015	1.41±1.10
	2	0.66±0.292	1.34±0.73
Gene 2	1	0.33±0.056	0.44±0.17
	2	0.61±0.478	1.22±1.10

Note: The signals were normalized against control *B2M* gene expression.

- Unbiased RNAseq in HepG2.2.15 cell line: 10 nM, 1000x EC₅₀

Unconjugated ALG-125755 10 nM



No cellular pathway affected

1 off target confirmed by 2nd independent experiment and qPCR

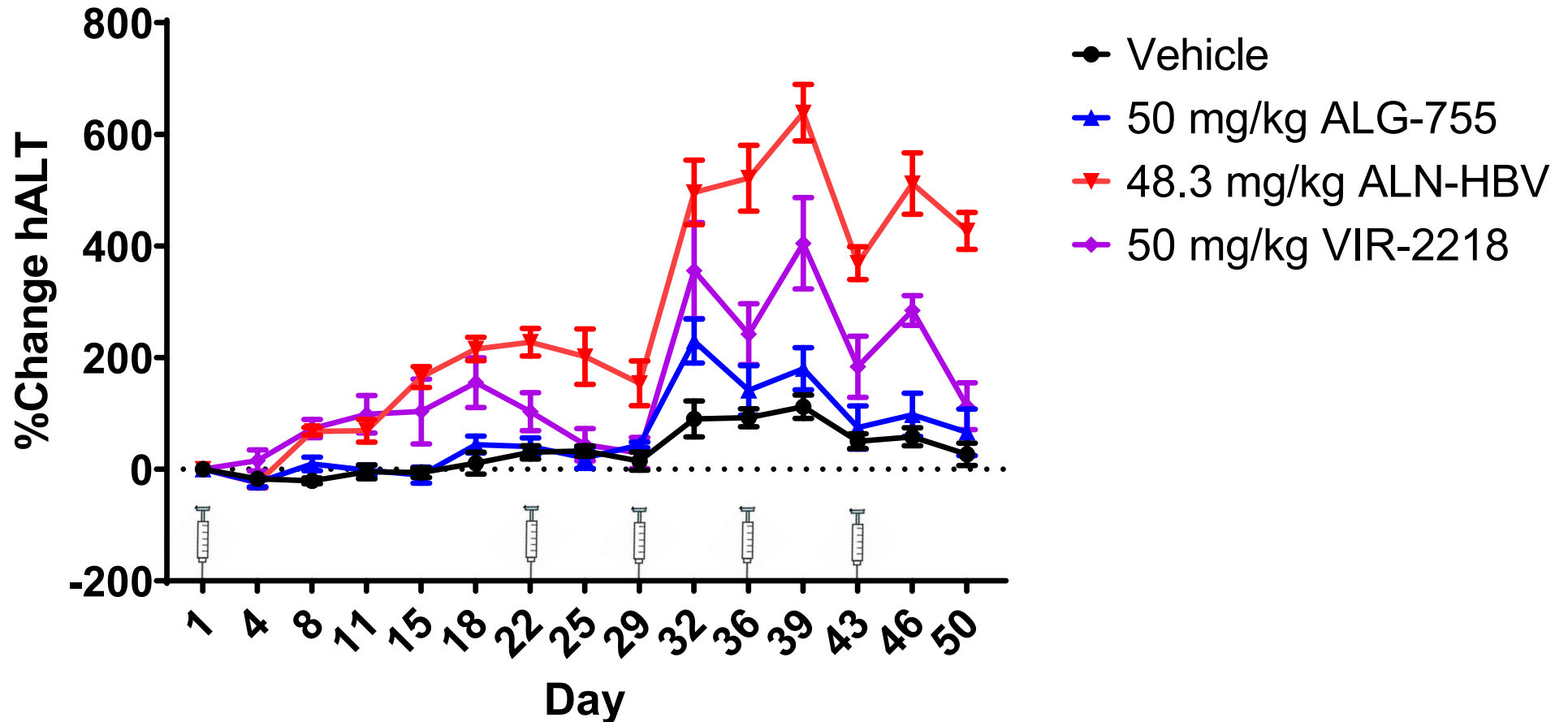
ALG-125755 FIH-enabling GLP Tox Studies

- Negative in the in vitro Ames and MNT studies
- Negative in rat MNT up to 2000 mg/kg
- No apparent changes in hemodynamic, ECG or respiratory parameters in monkeys or neurobehavioral findings in rats or monkeys up to 100 mg/kg, the highest dose tested
- Well tolerated in rat and monkey 5-week/6 dose repeat-dose tox studies with weekly subcutaneous doses of 0 (vehicle), 10, 30, 100 mg/kg/dose
 - The highest dose tested was the no observed adverse effect level (NOAEL) in both species

	NOAEL (mg/kg/dose)	C _{max} (µg/mL)	AUC _{0-24hr} (µg.hr/mL)
Rat	100	36	223
Monkey	100	17.5	271

Favorable nonclinical toxicology profile for ALG-125755

ALG-125755: Further De-risked Preclinically in PXB Mice with Humanized Livers



- 1) Confirmed ALN-HBV is hepatotoxic, VIR-2218 is not
- 2) ALG-125755 showed no evidence of hepatotoxicity as manifested by human ALT elevation

Short Interfering Nucleic Acid ALG-125755

Discovery and Advancement of a Differentiated siRNA

- siRNAs have demonstrated clinical validation in CHB infected patients
- We have designed our siRNA sequences using our proprietary technology and liver targeting conjugation to maximize in vitro and in vivo potency
 - Proprietary chemistries discovered to increase potency and stability/duration of action
 - Exclusive license to GalNAc technology applicable for liver targeting across oligo modalities
- Our siRNA approach may have safety, stability and potency advantages vs. competitor siRNAs
- Dosing in healthy volunteers was initiated in October 2022, dosing in CHB patients in December 2022

ALG-125755 is differentiated from potential competitors. HV and CHB patient dosing started Q4 2022

Acknowledgements

- Bioinformatics: Aneerban Bhattacharya, Antitsa Stoycheva
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THERAPEUTICS
