The CAM-E ALG-001075 Potently Reduces HBV cccDNA in Preclinical Experiments

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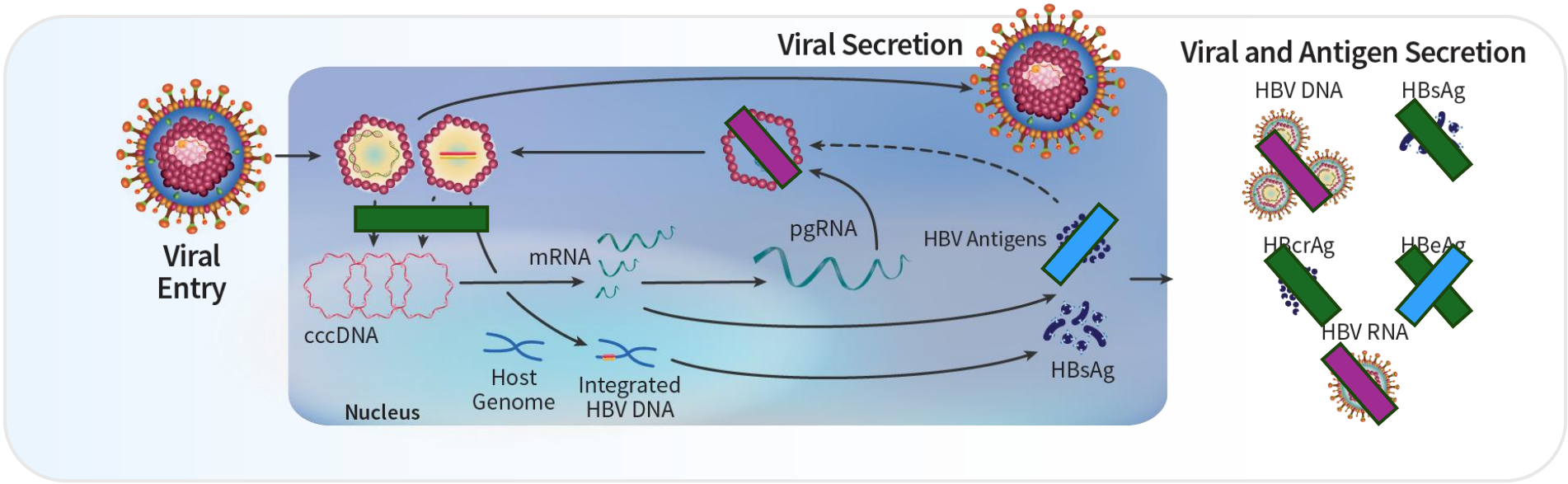
Capsid Assembly Modulators

Multiple Mechanisms of Action



- **CAMs bind to HBV core protein (HBc) and modulate capsid assembly**
  - CAM-E induce empty particles
  - CAM-A induce aberrant particles and cause HBc aggregation

- **CAM-E have 3 mechanisms of action:**
  - Primary MoA: Block pgRNA encapsidation
    - Block HBV DNA replication
  - Secondary MoA: Prevent capsid disassembly
    - Block cccDNA establishment
  - Third MoA: Direct effect on HBeAg

HBV capsid assembly is a key target for CHB treatment

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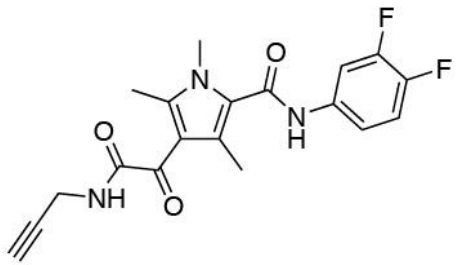
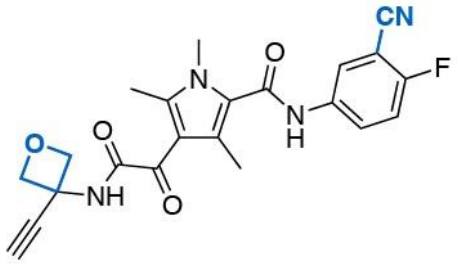
Discovery of ALG-000184

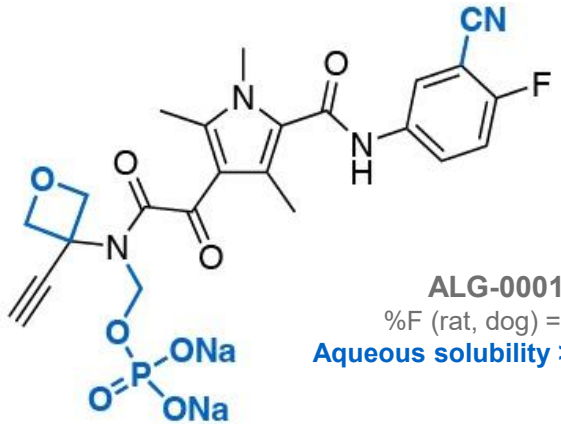
Prodrug of CAM ALG-001075



GLP-26
EC_{50} (HepG2.117) = 2.6 nM
Clearance (mouse) = **78.2** mL/min/kg
GSH adduct = **positive**



ALG-001075
EC_{50} (HepG2.117) = **0.63** nM
Clearance (mouse) = **12.0** mL/min/kg
GSH adduct = **negative**
%F (rat, dog) = **34**, **30**



ALG-000184
%F (rat, dog) = **48**, **84**
Aqueous solubility >100 mg/mL

Vendeville et al 2024, J Med Chem

- **CAM ALG-001075 was discovered at Aligos Therapeutics through optimization of Emory University's GLP-26**
- **ALG-000184 is a phosphate prodrug of ALG-001075 with improved oral bioavailability and solubility**
- **ALG-000184 has been dosed for up to 96 weeks in subjects with chronic HBV infection**
  - Well tolerated
  - Highly potent
  - No resistance under monotherapy seen in clinical studies to date

ALG-000184 Phase II clinical trial for viral suppression in subjects with chronic HBV infection initiated

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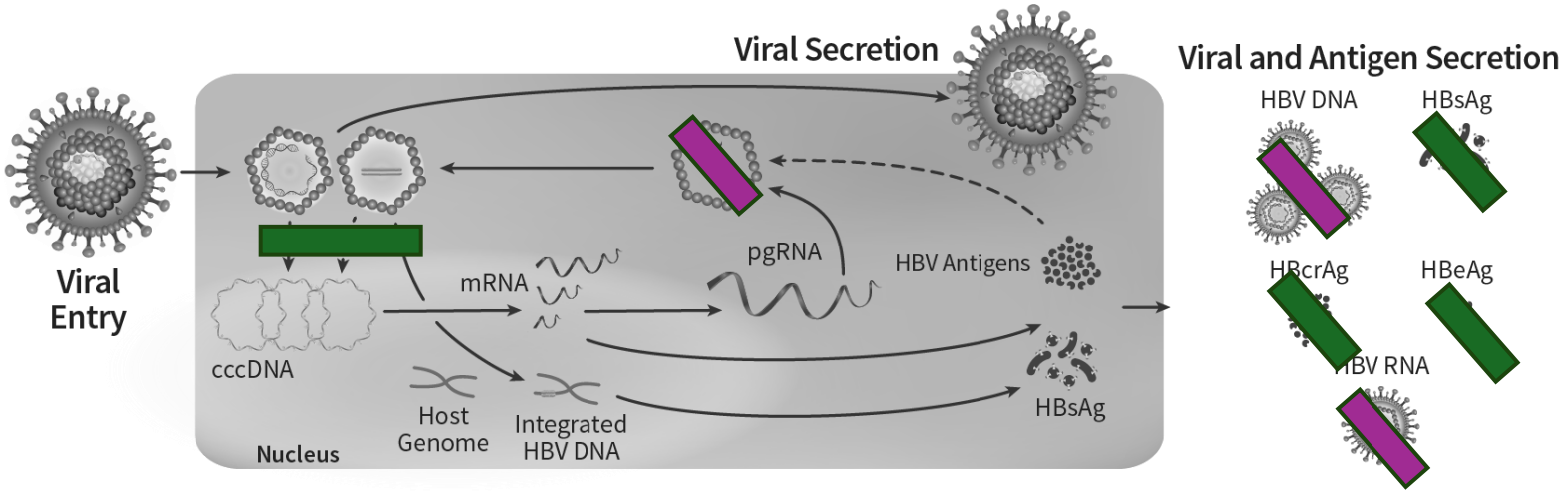
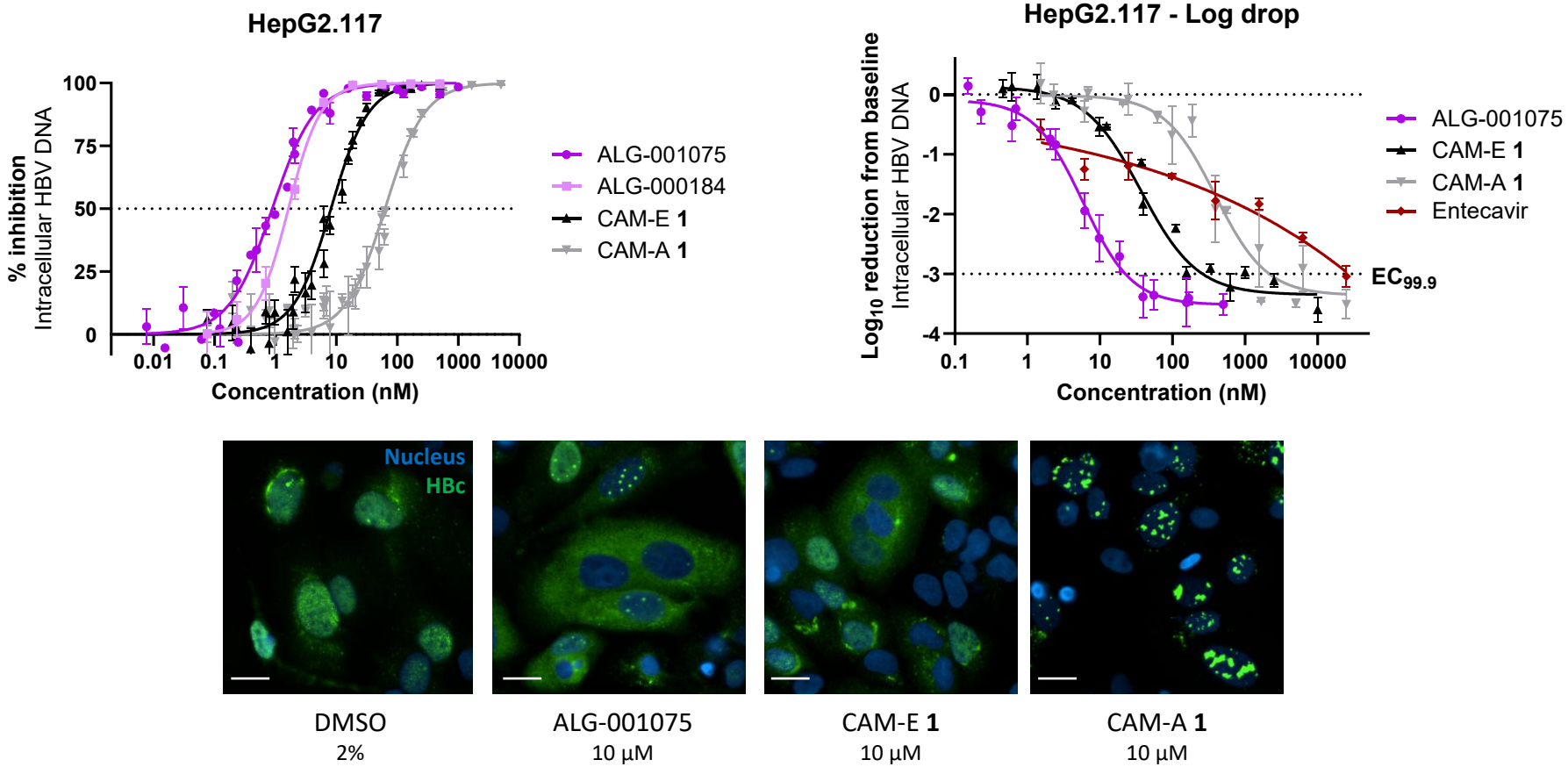
Study Objectives

- **Characterize the antiviral efficacy of CAM ALG-001075 on**
  - Primary MoA
    - HBV DNA
  - Secondary MoA
    - Directly: HBV cccDNA
    - Indirectly:
      - HBsAg
      - HBeAg
      - Intracellular HBV RNA
  - In different cellular systems
    - HepG2.117 cells
    - Primary human hepatocytes
    - HepG2-NTCP cells



ALG-001075

Primary MoA and CAM Classification

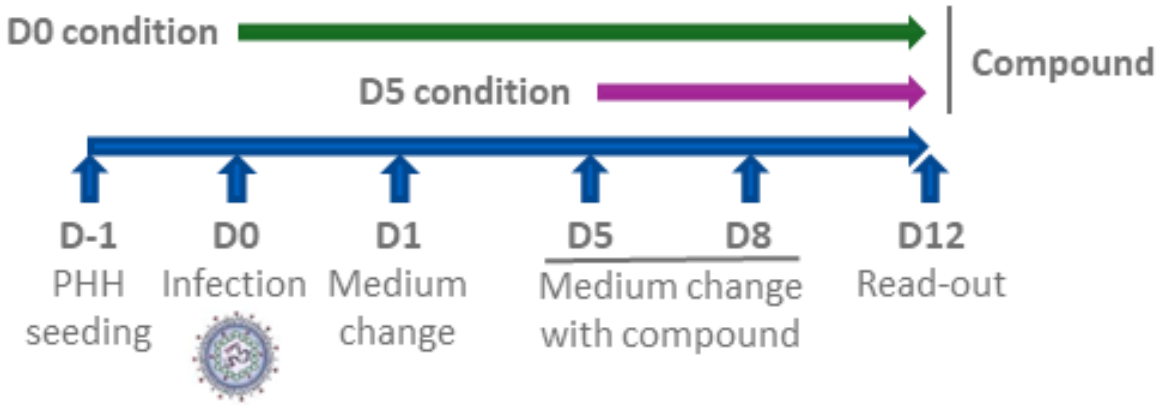


Evaluation in inducible HBV-expressing HepG2.117 cells (Sun & Nassal 2006, J Hepatol)
Data generated by Hannah Vanrusselt

ALG-001075 is a highly potent CAM-E with an EC_{50} of 0.63 nM and $EC_{99.9}$ of 22.3 nM

ALG-001075

Secondary MoA – Experimental Setup



Day 5 condition assesses primary MoA

Day 0 condition assesses secondary MoA

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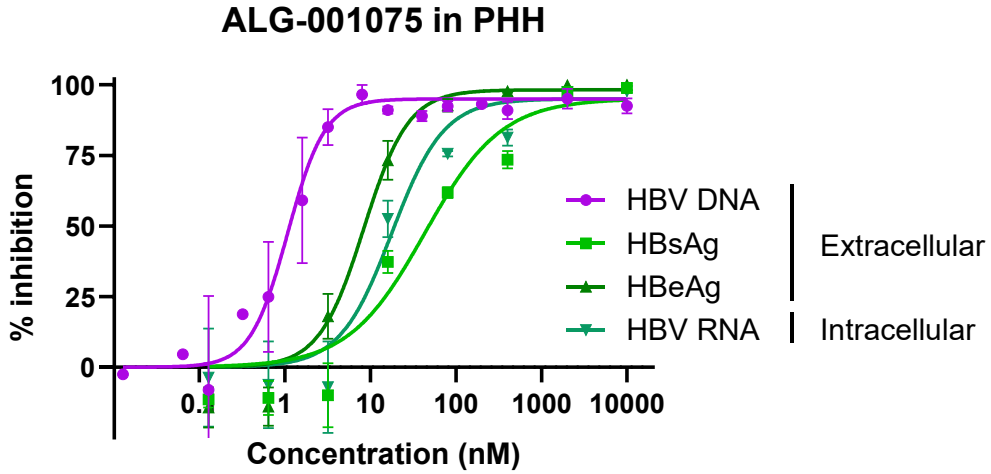
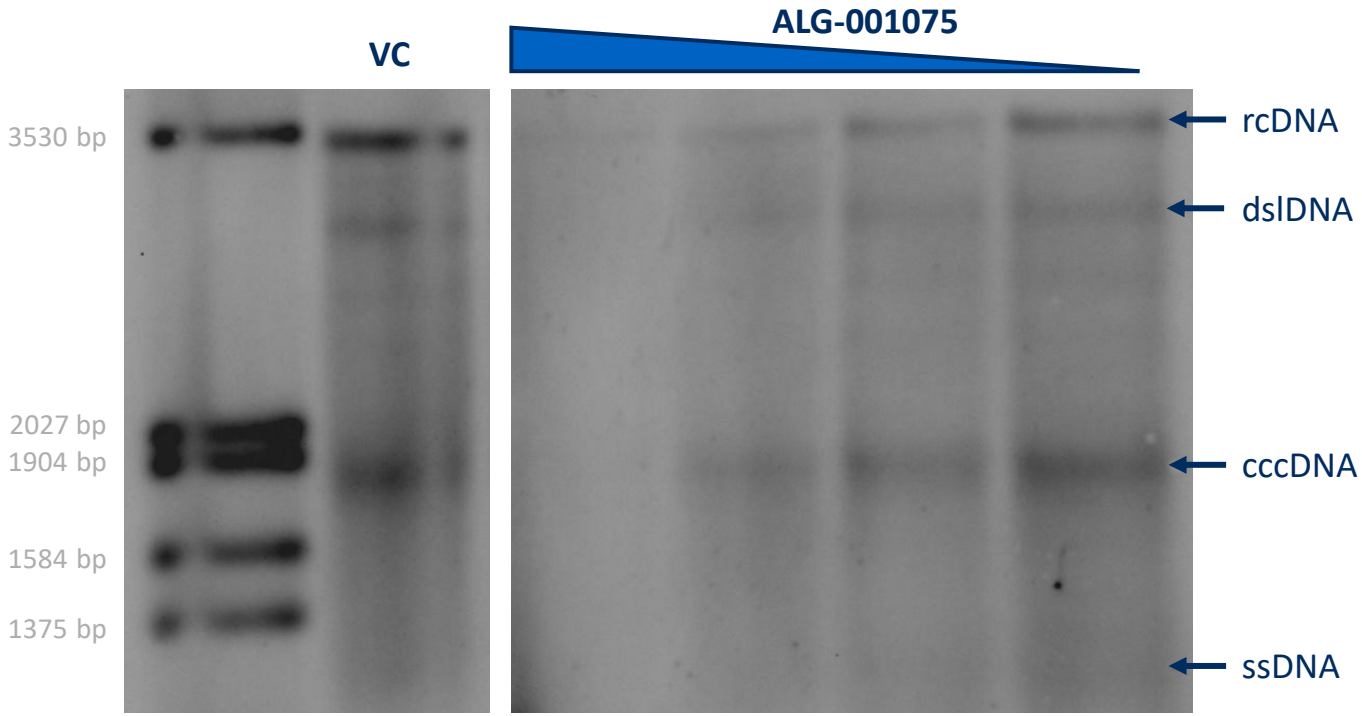
Secondary MoA – Effects on cccDNA Establishment

cccDNA-derived Markers



Southern Blot



Evaluation in primary human hepatocytes (left) and HepG2-NTCP cells (right) with compound included at the time of infection
cccDNA, covalently closed circular DNA; dslDNA, double-stranded linear DNA; PHH, primary human hepatocytes; rcDNA, relaxed circular DNA; ssDNA, single-stranded DNA; VC, virus control
Data generated by Hannah Vanrusselt & Jordi Verheyen

ALG-001075 effectively inhibits cccDNA establishment in vitro

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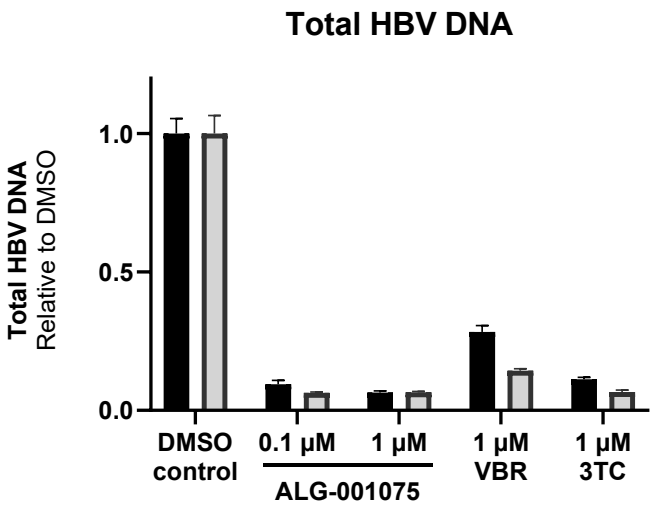
ALG-001075

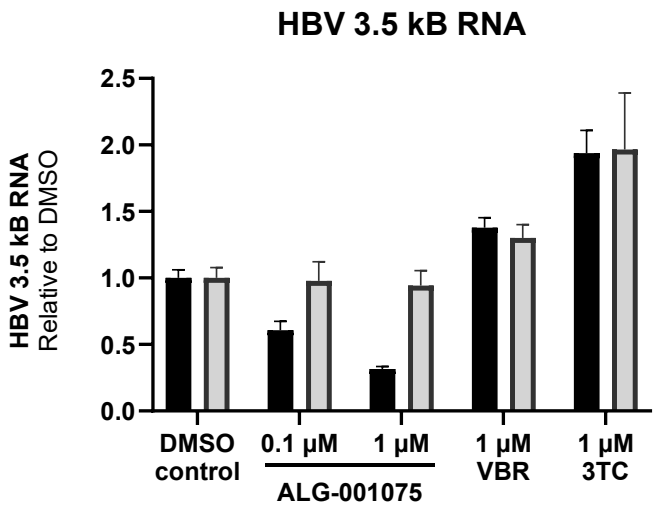
External Validation by Barbara Testoni – Fabien Zoulim Group

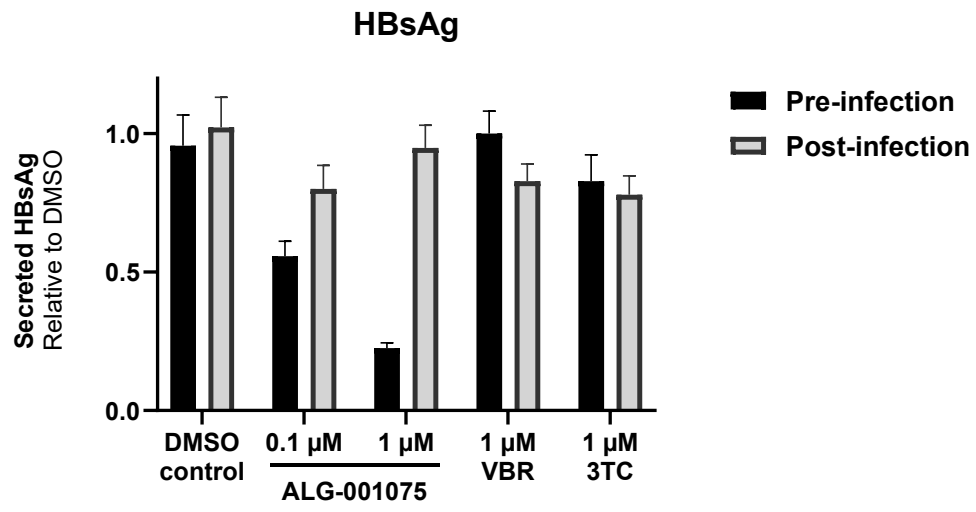
HepG2-NTCP Cells

Primary MoA

Secondary MoA







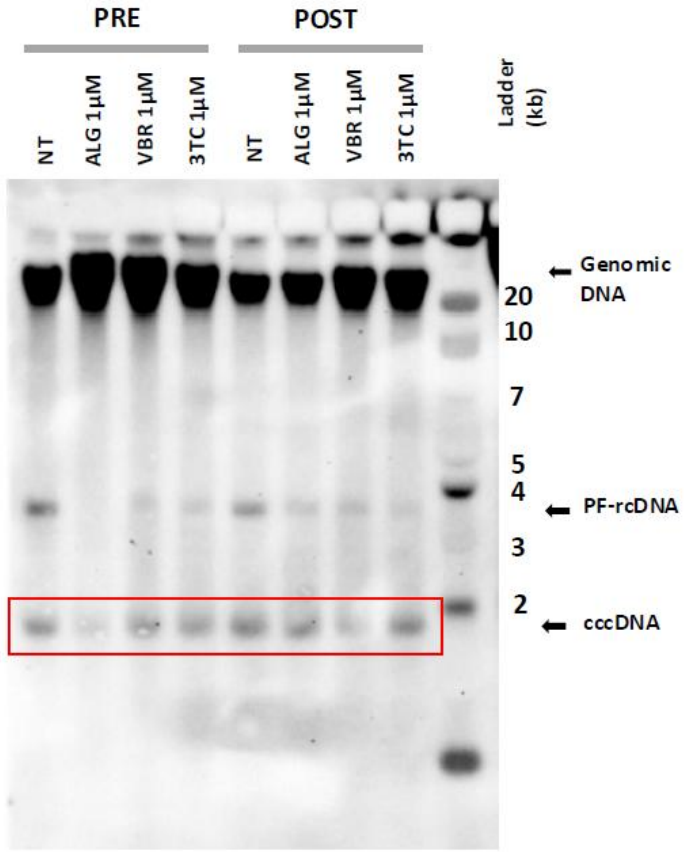
VBR, vebicorvir; 3TC, lamivudine
Data generated by Audrey Diederichs

Primary mechanism of action of ALG-001075 confirmed

Secondary mechanism of action confirmed through surrogate markers

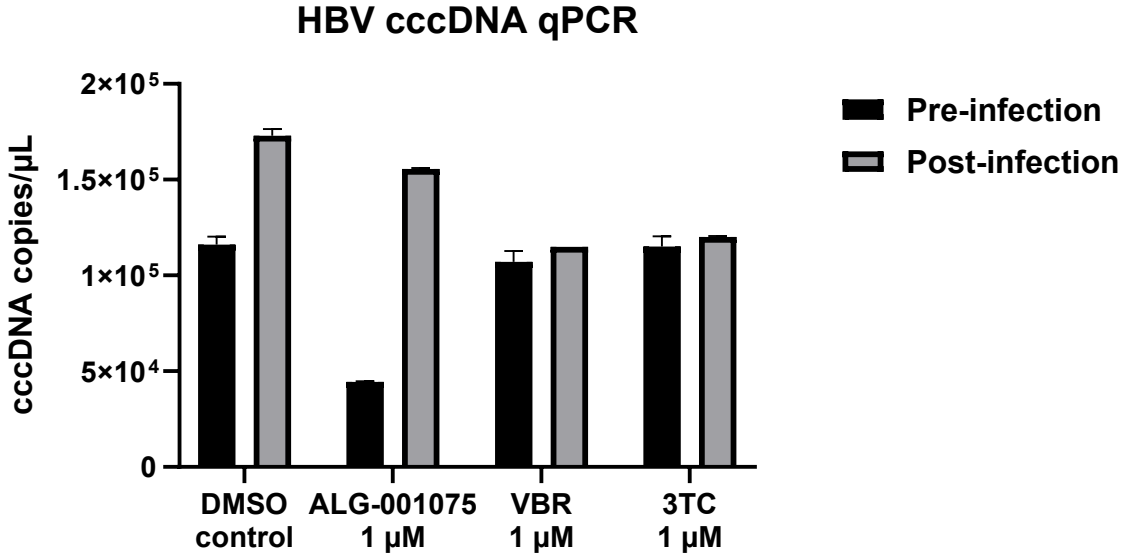
ALG-001075

External Validation by Barbara Testoni – Fabien Zoulim Group



HepG2-NTCP Cells

Secondary MoA



ALG, ALG-001075; NT, not treated; PF-rcDNA, protein-free relaxed circular DNA; VBR, vebicorvir; 3TC, lamivudine
Data generated by Maud Michelet

ALG-001075 prevents cccDNA establishment when added at time of infection

Results were confirmed in HepaRG cells

Clinical Translation?

ALG-000184 in Subjects with Chronic HBV Infection

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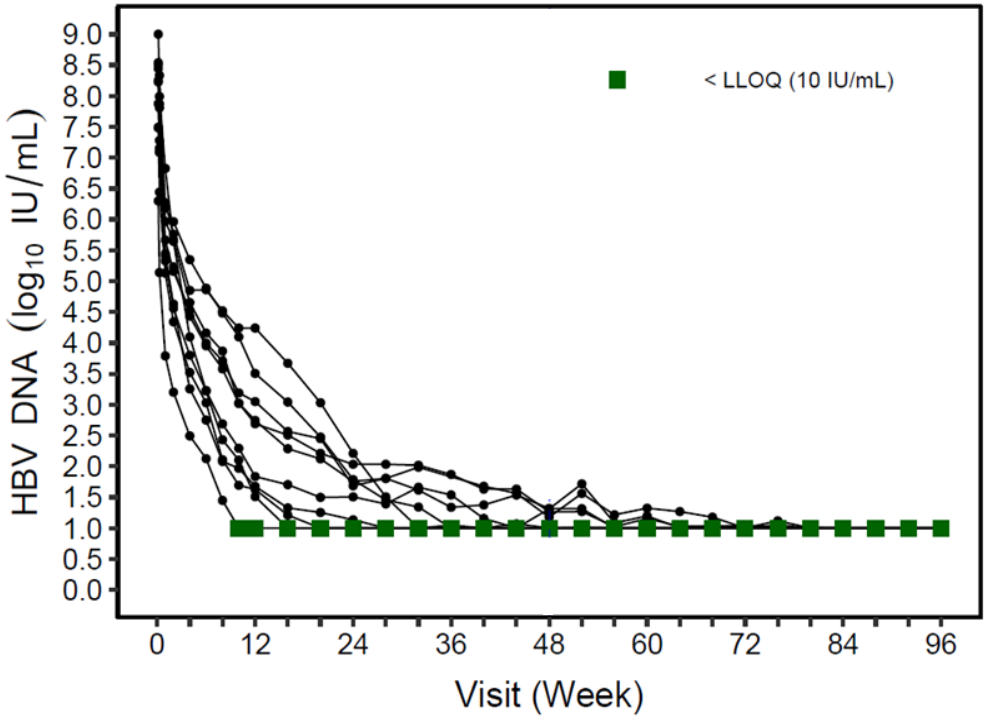
ALG-000184

Clinical Translation – Primary Mechanism

- **ALG-000184 300 mg QD monotherapy in HBeAg-positive subjects**



Total n	10	10	10	9	10	10	10	10	9
< LLOQ [10 IU/mL]	0	1	2	5	6	7	9	10	9
< LLOD [≤ 4.29 IU/mL]	0	0	0	0	0	0	2	3	5

Yuen MF et al, EASL 2025
LLOD, lower limit of detection; LLOQ, lower limit of quantification

All subjects had HBV DNA levels below LLOQ before week 96

No viral breakthrough under monotherapy seen in clinical studies to date

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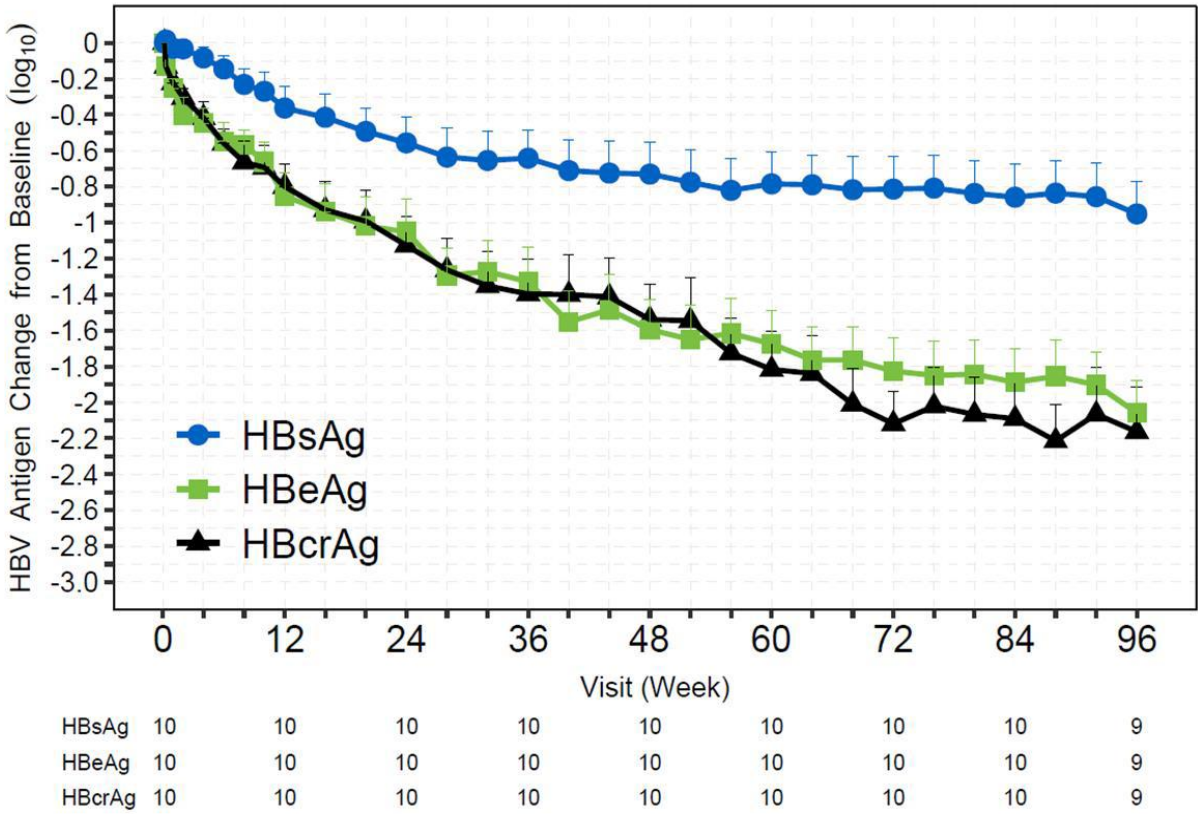
ALG-000184

Clinical Translation – Secondary and Third Mechanism

- **ALG-000184 300 mg QD monotherapy in HBeAg-positive subjects**



Yuen MF et al, EASL 2025
HBcrAg, HBV core-related antigen

Continued substantial reductions of HBsAg, HBeAg and HBcrAg through week 96

Likely driven by prevention of cccDNA establishment and direct HBeAg effect

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ALG-001075 and ALG-000184

Conclusions

- **ALG-001075 is among the most potent CAMs reported to date, both on**
  - Primary MoA: HBV DNA, RNA
  - Secondary MoA: cccDNA
- **Prodrug ALG-000184 showed potential engagement of the secondary mechanism of CAMs for the first time in the clinic, including HBsAg, HBeAg and HBcrAg reductions**
- **A phase II clinical trial for ALG-000184 was initiated in August 2025**

B SUPREME

- **Posters on Aligos CAMs at the meeting:**
  - #283: Differential impact of CAM-E and CAM-A on hepatitis B core protein phosphorylation states in vitro
    - Hannah Vanrusselt, in collaboration with Abbott
  - #285: Capsid assembly modulators bind and directly target HBeAg
    - Jordi Verheyen

Thank You!

- **Aligos Therapeutics**

- **Aligos Belgium**

- **UMR 1350 PaThLiv, Lyon**

- **The HBV group**

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Pathobiology and Therapy of Liver Diseases

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