

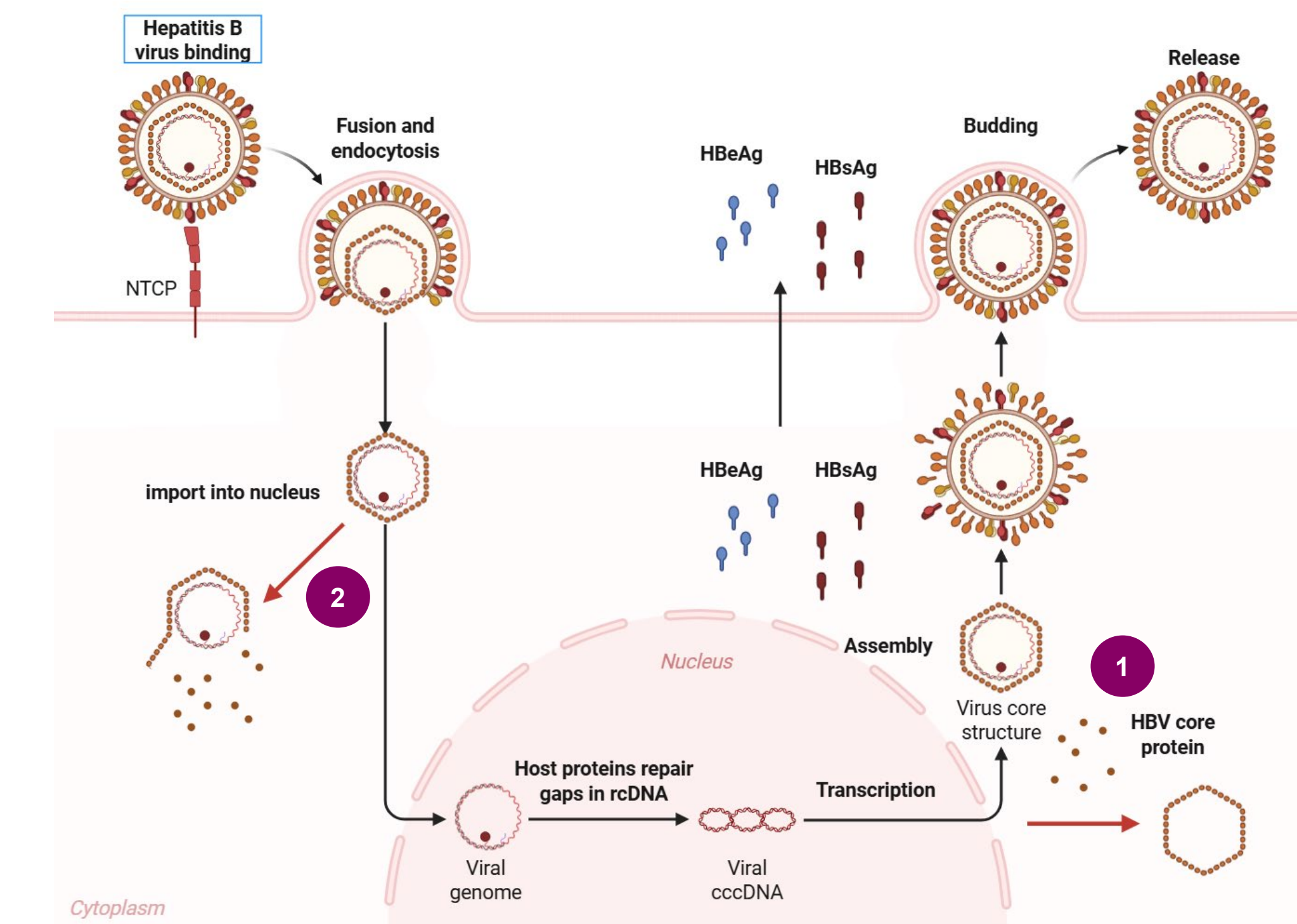


Background¹⁻⁴

- Chronic hepatitis B (cHBV) affects ~240 million people worldwide and causes ~1.1 million deaths annually from cirrhosis and hepatocellular carcinoma.
- Nucleos(t)ide analogues suppress HBV DNA but cannot eliminate covalently closed circular DNA (cccDNA), necessitating lifelong therapy
- Capsid assembly modulators (CAMs) act through two mechanisms — induction of the assembly of empty capsids (MOA #1) and disruption of incoming mature capsids (MOA #2)
- Both 1st gen and next-gen CAMs inhibit by MOA #1, while only next-gen CAMs potentially inhibit by MOA #2
- ABI-4334, a next-generation CAM, shows increased *in vitro* potency in inducing capsid assembly and disruption of incoming mature capsids

Here we present preclinical SAR and a mechanistic rationale to explain the improved activity in disruption of mature incoming capsids

Inhibition of HBV by CAMs



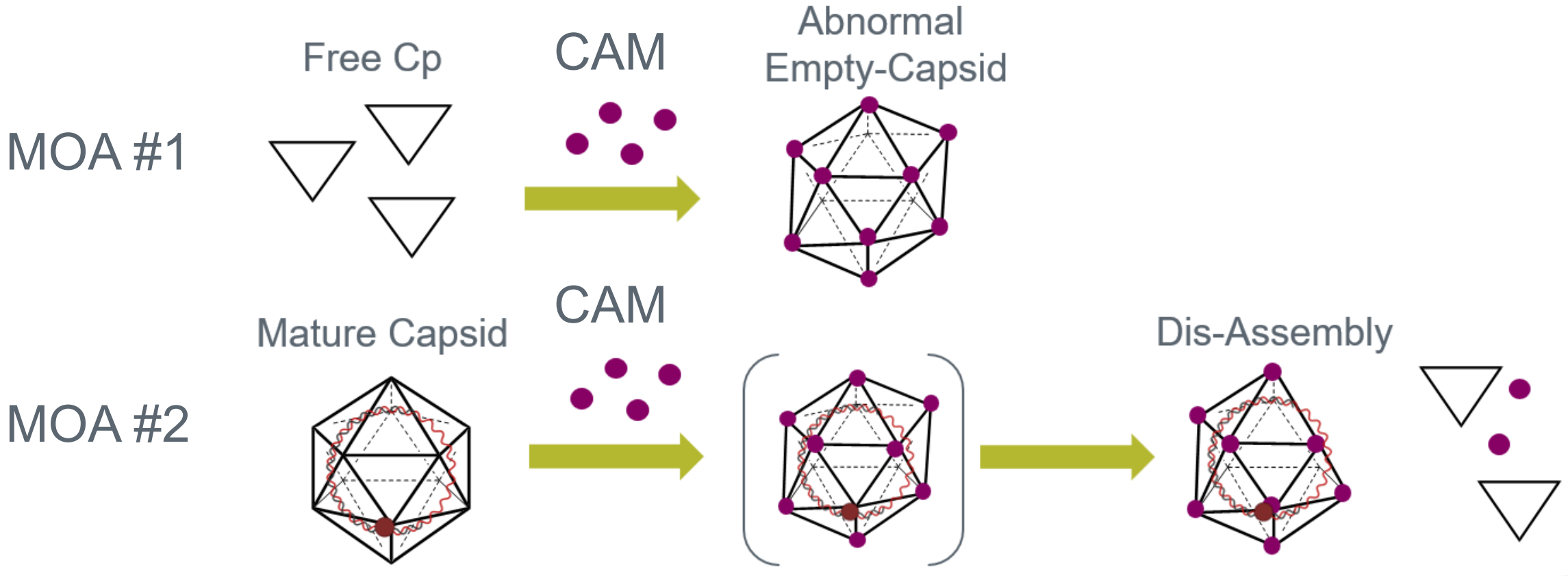
- CAM-induced assembly of empty capsids (MOA #1)**
 - cccDNA formation and gene expression not affected
 - No rcDNA formation
 - Result: reduced HBV secretion
 - Assay:** measure HBV DNA in stably transfected cells (VL-EC₅₀)
- CAM-induced disruption of mature capsid (MOA #2)**
 - Incoming HBV DBA never reaches nucleus
 - Result: reduced cccDNA, pgRNA, HBeAg, HBsAg
 - Assay:** HBeAg expression by ELISA (HBeAg EC₅₀)

References 1) European Association for the Study of the Liver. *J Hepatol.* 2017;67:370-98. 2) World Health Organization. *Hepatitis B Factsheet* 2025. Geneva: World Health Organization; 2025. 3) World Health Organization. Key facts. 2021. <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b>. Accessed on October 29, 2025. 4) El-Serag HB, et al. *Gastroenterology.* 2012;142:1264-73

Abbreviations: CAM, capsid assembly modulator; cccDNA, covalently closed circular DNA; FaSSIF, fasted state simulated intestinal fluid; FeSSIF, fed state simulated intestinal fluid; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B s-antigen; NrtI, nucleoside reverse transcript inhibitor; pgRNA, pregenomic RNA; rcDNA, relaxed circular DNA

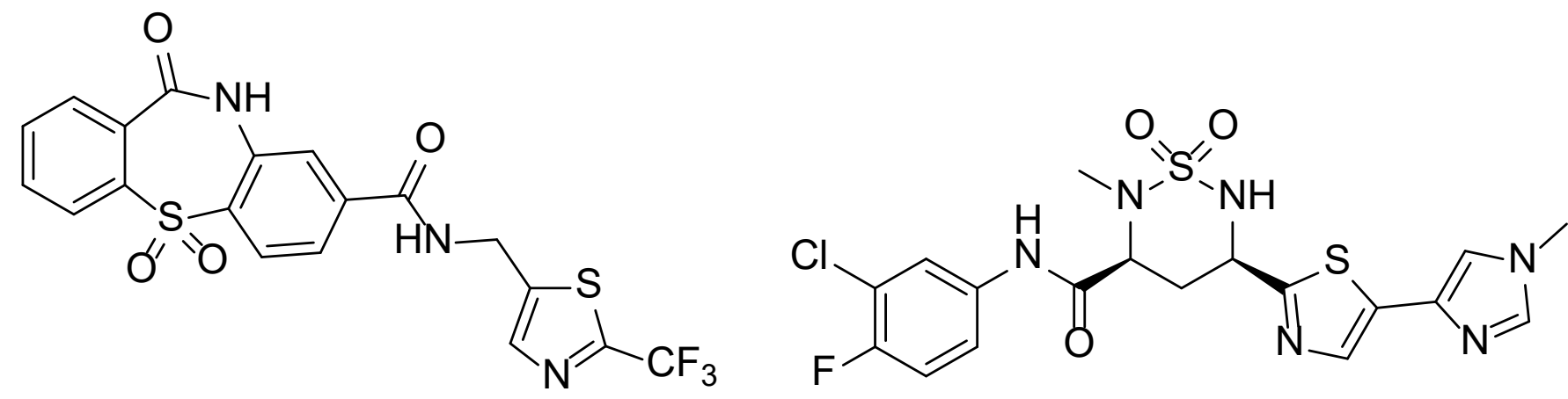
Mechanistic Paradox of CAMs

One binding site, two mechanisms



- CAM induces assembly of empty capsids which are stable but structurally skewed
- Mature capsids are more strained due to the presence of rcDNA
- CAM binding places more strain on the mature capsid leading to disruption

1st Generation CAMs

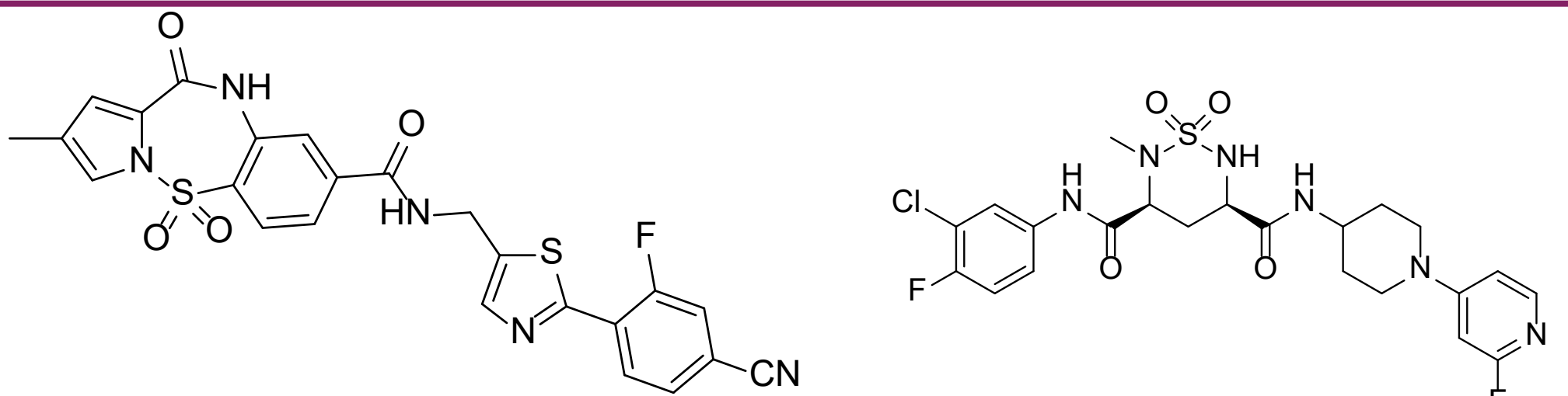


	vecicorvir ^s	firzacorvir ^s
MOA #1, VL EC ₅₀ (nM)	173	22
MOA #2, HBeAg EC ₅₀ (nM)	5,447	467
EC ₅₀ ratio	31	21

- Significant reduction in HBV DNA and RNA observed in clinical trials
- 1st Generation inhibitors show at least a 20-30 fold difference in activity between MOA #1 and MOA #2

References 5) Huang Q. et al. *Antimicrobial Agents and Chemother.* 2020. 64, e01463 6) Yan, R. et al. *Antiviral Res.* 2023, 209, 105485.

Optimized 1st Generation CAMs

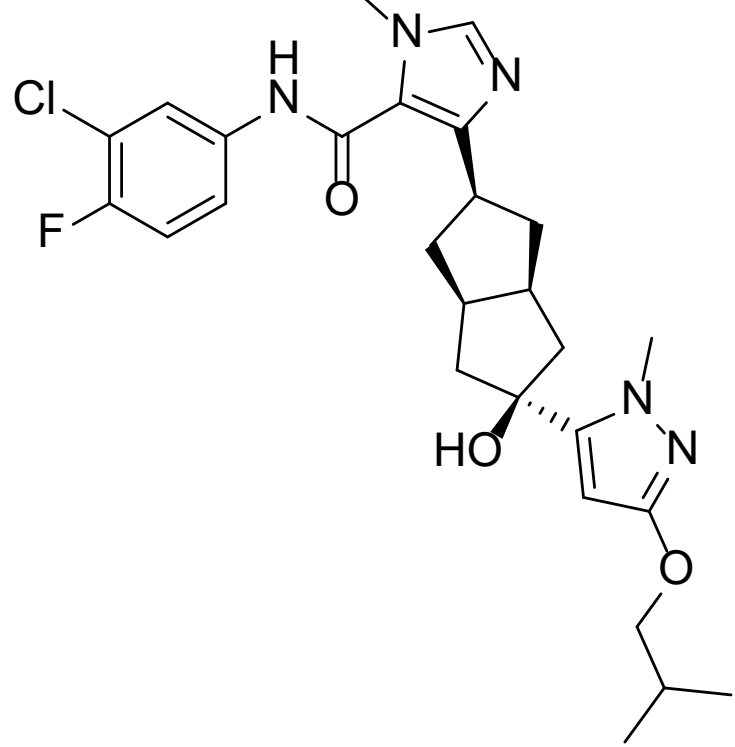


	AB-871	AB-909
MOA #1, VL EC ₅₀ (nM)	8	1
MOA #2, HBeAg EC ₅₀ (nM)	700	2,910
EC ₅₀ ratio	88	2,910

- Optimization of 1st gen CAMs yields improved activity in MOA #1
- MOA #2 does not track well with MOA #1 resulting in higher EC₅₀ ratio

ABI-4334 a next generation CAM

Improved correlation between MOA #1 and MOA #2



	ABI-4334
MOA #1, VL EC ₅₀ (nM)	0.5
MOA #2, HBeAg EC ₅₀ nM	2.6
EC ₅₀ ratio	5
Serum shift in EC ₅₀	5.5x

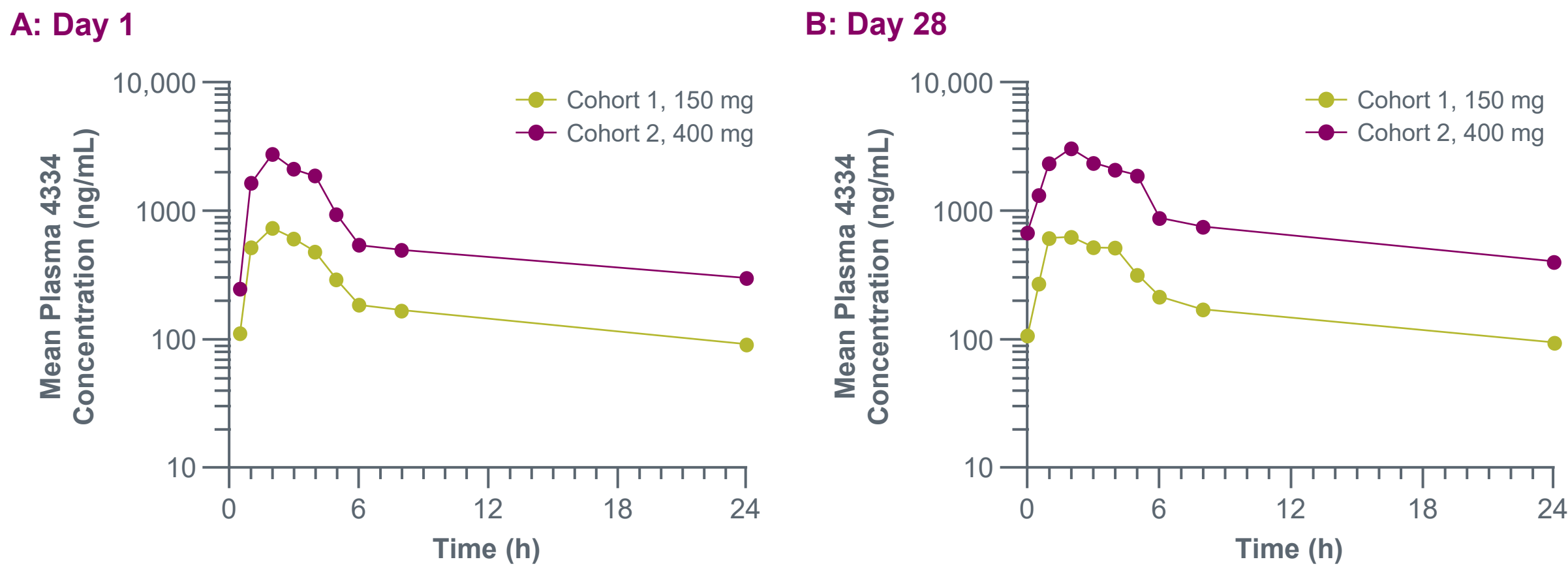
	Rat	Dog	Monkey
F _{po} (%)	46	93	24
CL (mL/min/kg)	15.2	3.63	7.29
V _{ss} (L/kg)	2.63	3.17	2.42
T _{1/2} (h)	2.68	16.8	5.67

Assay	Result
% hPPB	89.6
Sol. FaSSIF (pH 6.5)/FeSSIF (pH 5.0) (µg/mL)	55/672
hHep Cl _{int} (mL/min/kg)	12.1
hHep Cl _{int} (mL/min/kg)	2.7
Caco-2 P _{app} A-B (cm/s)	4 x 10 ⁻⁶
Rat Liver/Plasma ratio	7.8

Phase 1b Clinical Trial

28 Days in HBeAg⁺ and HBeAg⁻ patients

Jucov et al. AASLD, The Liver Meeting 2025; Washington DC, November 7-11, 2025

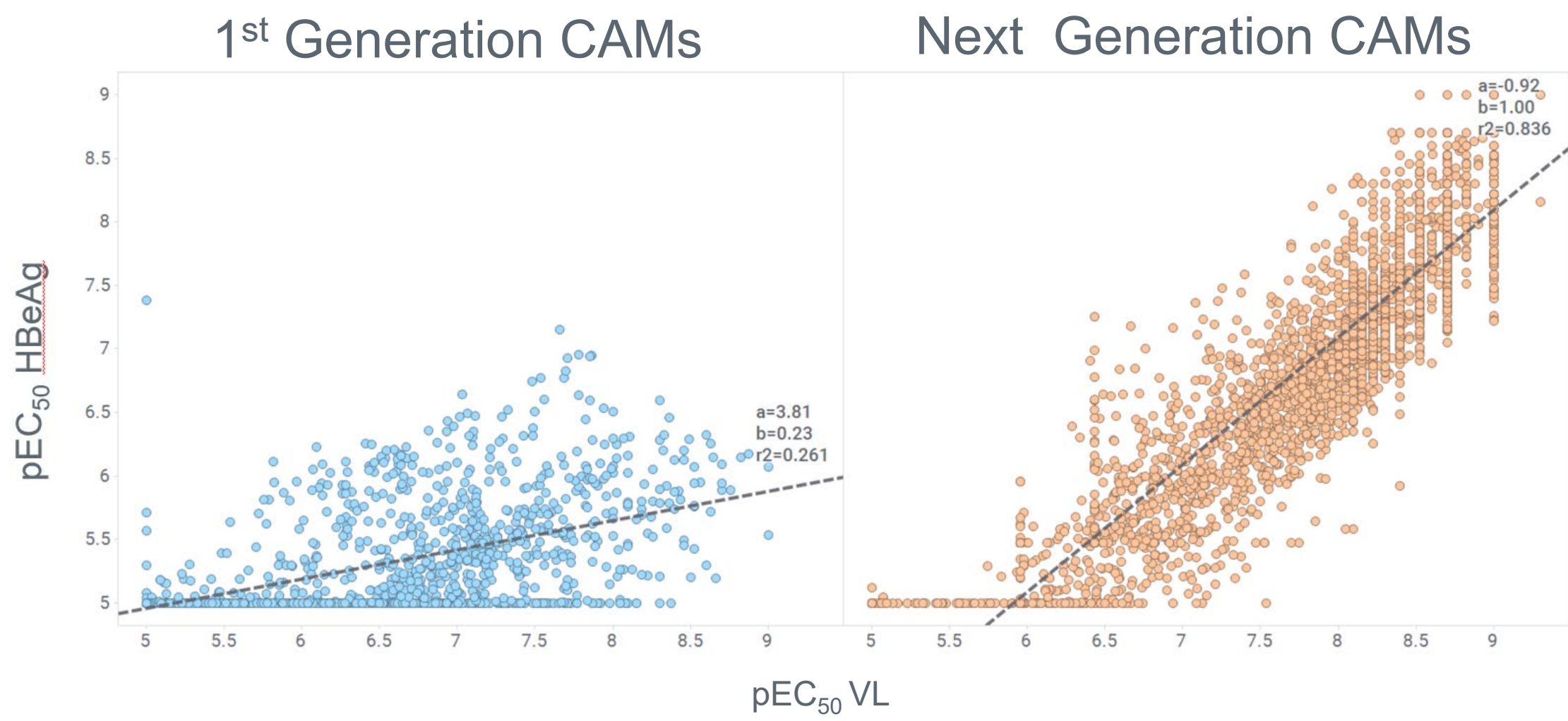


- ABI-4334 was rapidly absorbed, with mean T_{1/2} of 17.5 to 27.5 hours
- Mean steady-state concentrations at 24 hours post dose at the 150 mg and 400 mg dose levels were approximately 62- to 269-fold above serum binding adjusted VL EC₅₀ and approximately 12- to 52-fold above serum binding adjusted HBeAg EC₅₀

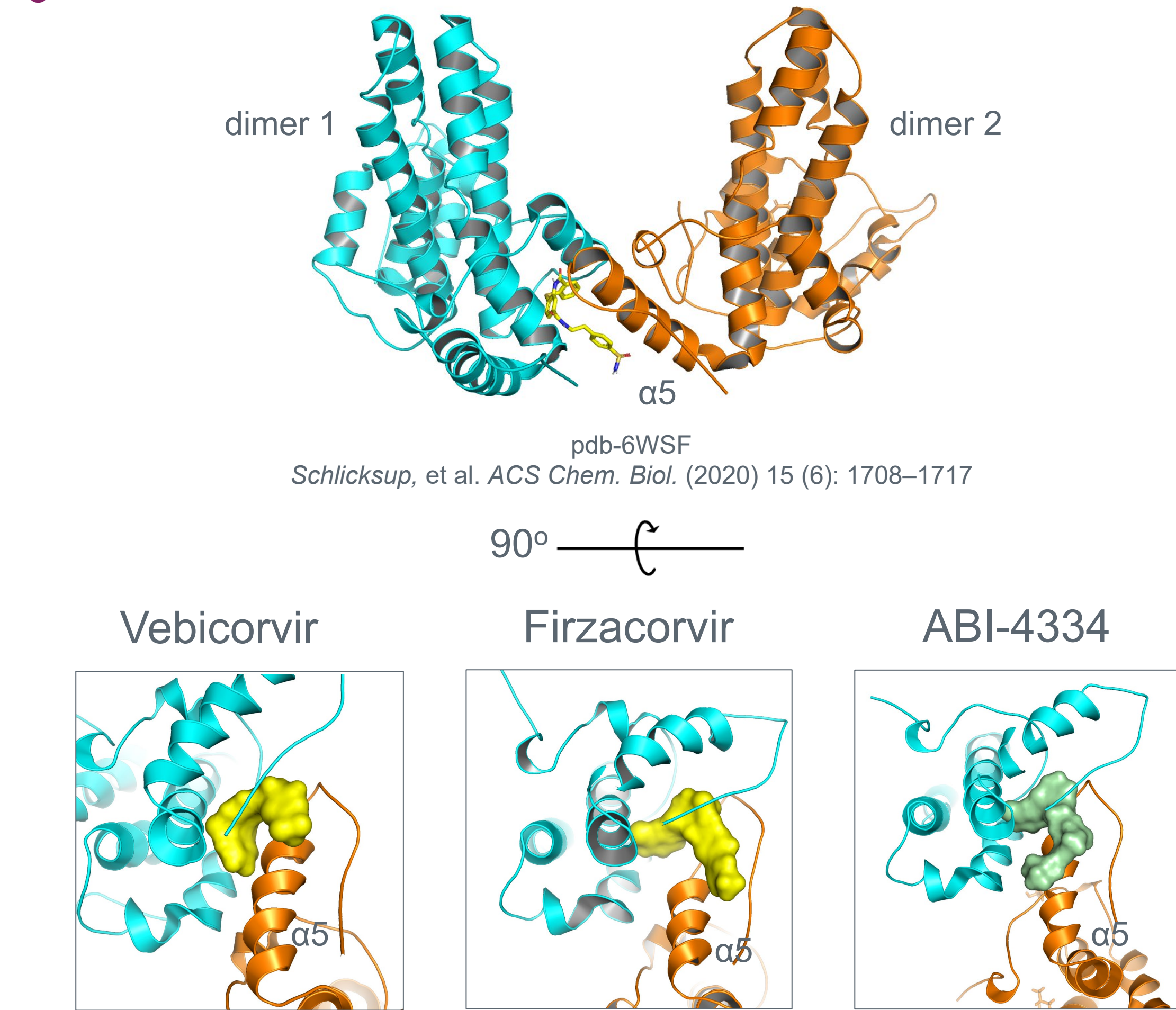
HBeAg Status at Baseline	Mean (SD) [n] Change From Baseline to Day 28								
	HBV DNA (log ₁₀ IU/mL)			HBV pgRNA (log ₁₀ U/mL)			HBeAg (log ₁₀ IU/mL)		
	150 mg QD	400 mg QD	PBO QD	150 mg QD	400 mg QD	PBO QD	150 mg QD	400 mg QD	PBO QD
HBeAg-negative	-2.7 (0.58) [n=6]	-3.1 (0.59) [n=7]	-0.1 (0.20) [n=2]	-1.1 (1.52) [n=7]	-0.6 (1.09) [n=7]	0.3 (0.36) [n=2]	-0.1 (0.11) [n=6]	0.0 (0.06) [n=2]	0.0 (0.05) [n=2]
HBeAg-positive	-3.6 (0.35) [n=2]	-3.5 (NA) [n=1]	-0.1 (0.11) [n=2]	-1.9 (2.23) [n=2]	-2.8 (NA) [n=1]	0.0 (0.20) [n=2]	-0.1 (0.02) [n=2]	-0.2 (NA) [n=1]	0.0 (0.10) [n=2]
Combined HBeAg-negative and -positive	-2.9 (0.66) [n=8]	-3.2 (0.56) [n=8]	-0.1 (0.13) [n=4]	-1.3 (1.57) [n=8]	-0.9 (1.27) [n=8]	0.1 (0.27) [n=4]	-0.1 (0.10) [n=8]	0.0 (0.08) [n=8]	0.0 (0.06) [n=4]

- In HBeAg-negative participants, the mean Day 28 changes were as follows:
 - HBV DNA: -2.7 and -3.1 log₁₀ IU/mL for 150 mg and 400 mg, respectively
 - HBV pgRNA: -1.1 and -0.6 log₁₀ U/mL for 150 mg and 400 mg, respectively
 - No changes in HBeAg were observed

SAR of VL EC₅₀ versus HBeAg EC₅₀



Mechanistic Rationale



- Compounds manually docked in using pdb-6WSF as reference
- Model suggest different inhibitor interaction with α5-helix of dimer 2

Summary

- ABI-4334 is potent in both CAM mechanisms — empty-capsid assembly (VL EC₅₀ 0.5 nM) and disruption of incoming mature capsids (HBeAg EC₅₀ 2.6 nM) — an EC₅₀ ratio of ~5 vs. ≥20× for prior CAMs.
- A tight VL-HBeAg EC₅₀ correlation across next-generation CAMs shows both mechanisms were co-optimized, not traded off.
- Docking (pdb-6WSF) links the improved mature-capsid disruption to an altered α5-helix (dimer 2) contact that further strains the mature capsid.
- Favorable cross-species oral PK supported a Phase 1b readout: HBV DNA -2.7/-3.1 log₁₀ (150/400 mg QD) with pgRNA reductions in HBeAg- and HBeAg+ patients.