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HBV/HDV-ACT Connect
(ADVANCING CURATIVE TREATMENTS)

Emerging Concepts and Data CpAMS Third and Fourth Generation

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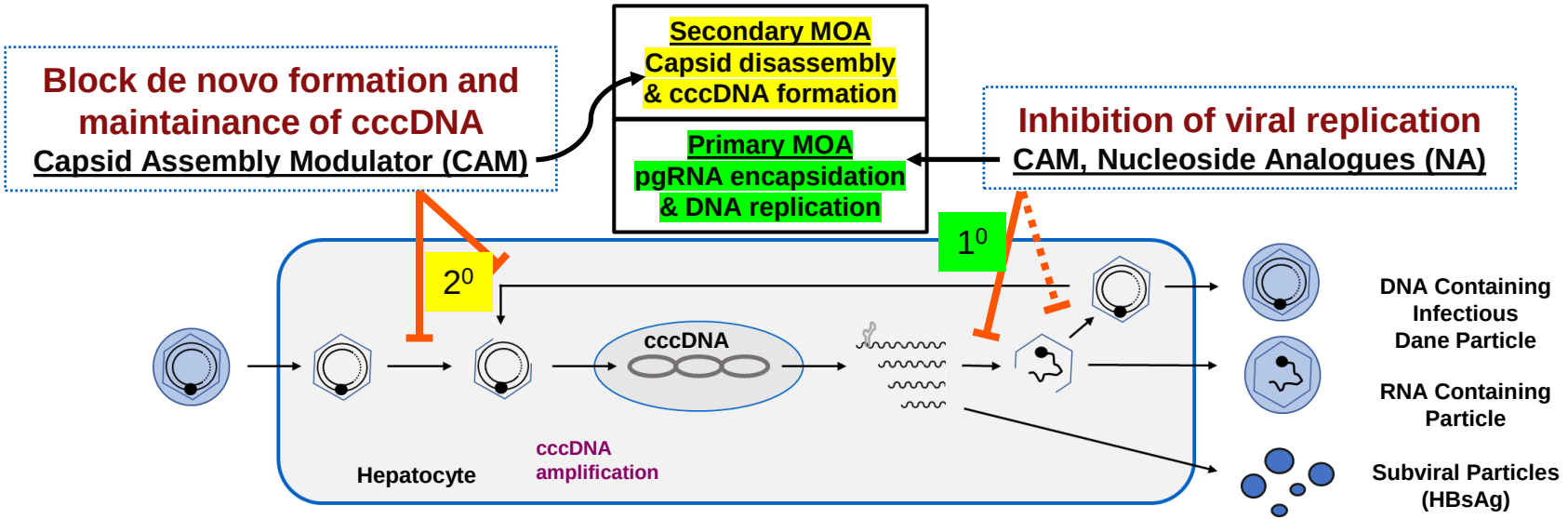
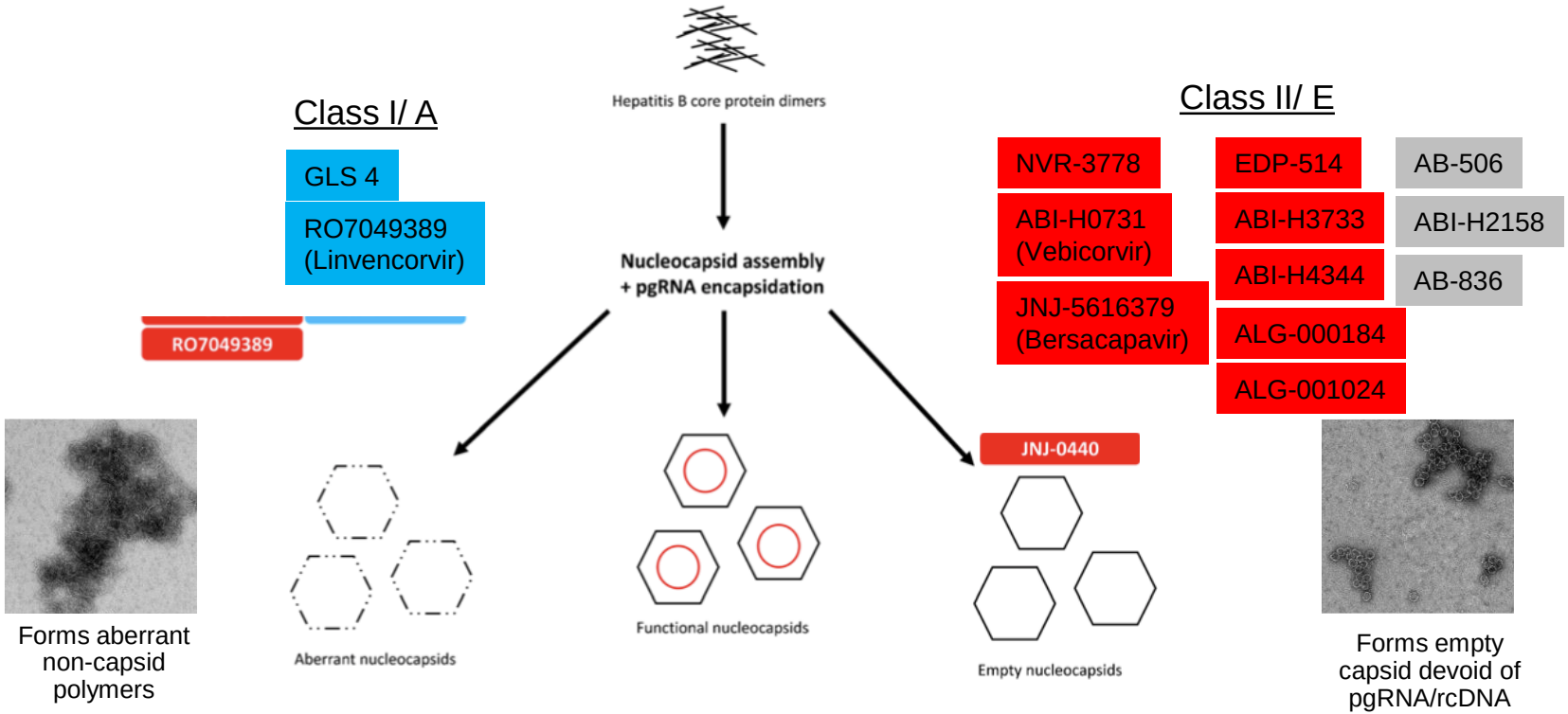
- Agents discussed in this talk are non-FDA approved and/ or indications

Core Protein Allosteric Modulator (CpAM): Modes of Action



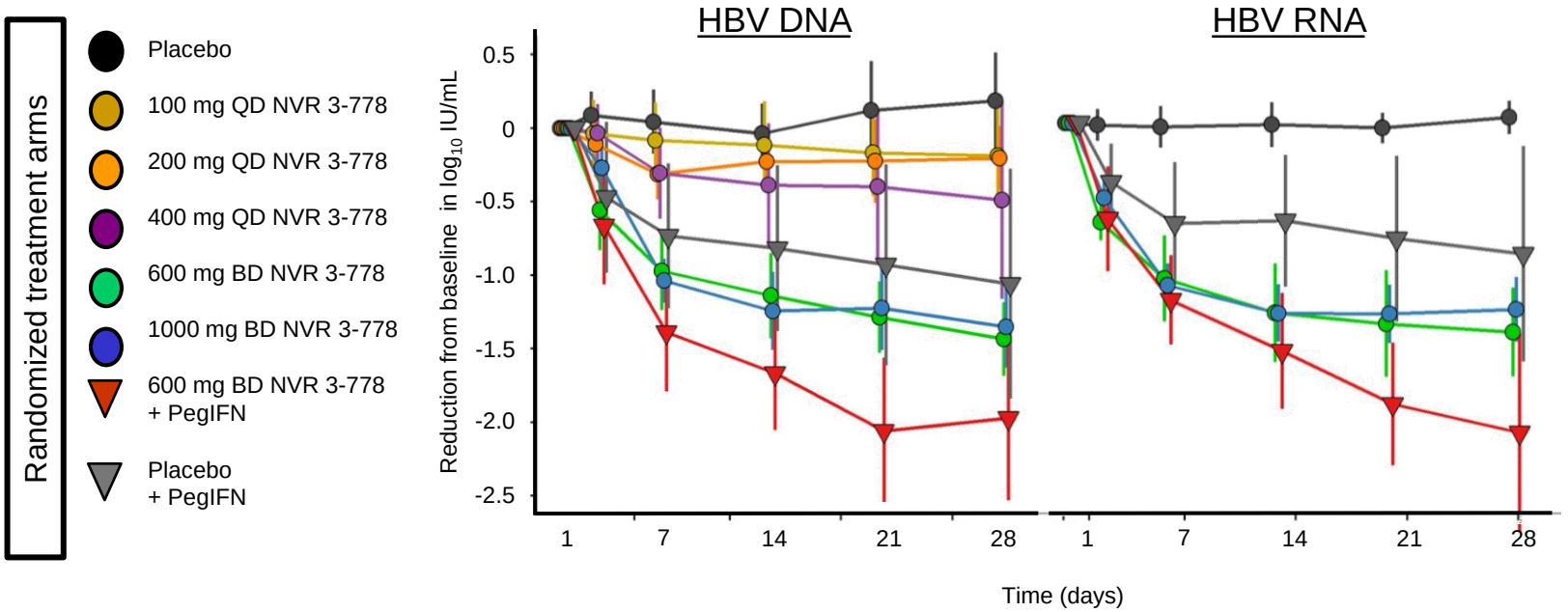
Adapted from L. Blatt, HepDart. 2017.

Two Classes of CpAM



Adapted from Hui R, Yuen MF. *Curr Hepatol Reports*. 2020;19:293-301.

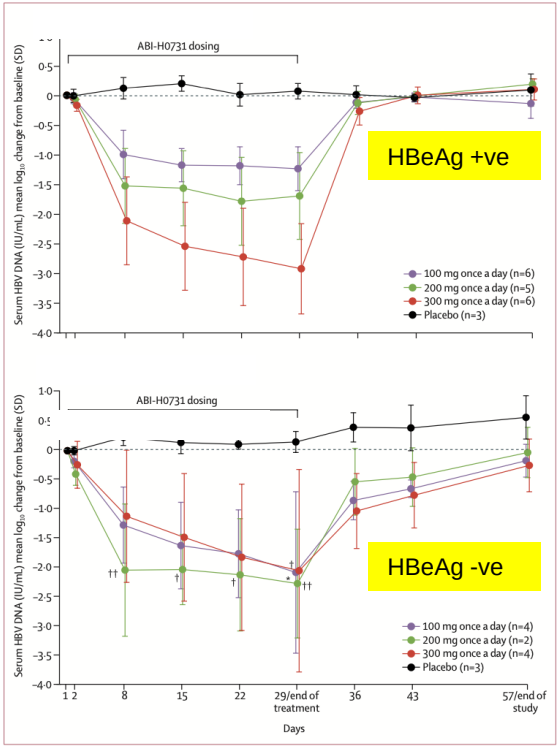
First-In-Class (1st Generation): NVR-3778 for 4 Weeks +/- Peg IFN



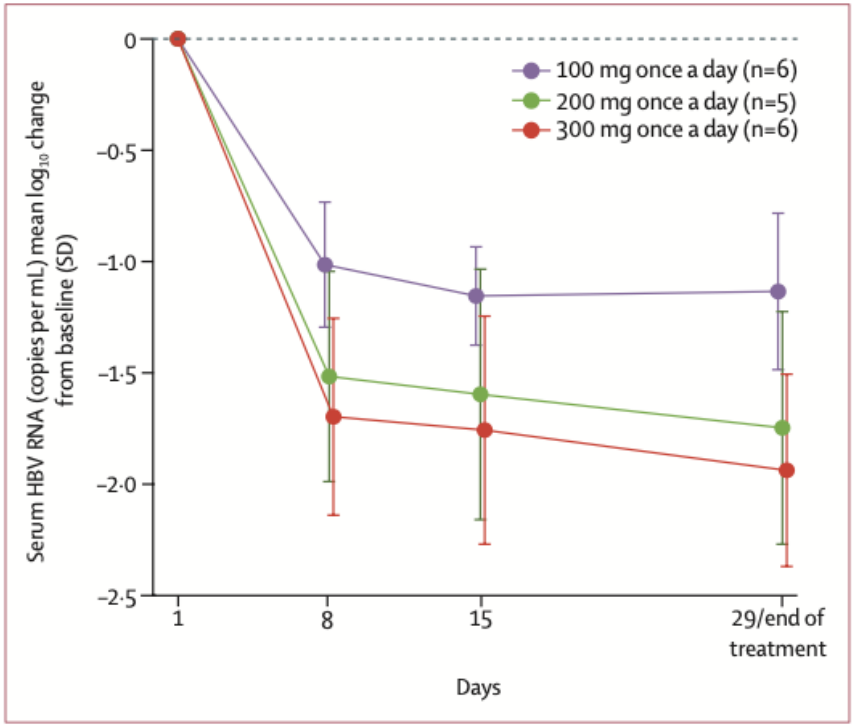
Yuen MF et al. *Gastroenterology*. 2019;156:1392-403.

1st/2nd Generation: ABI-H0731 (Vebicorvir) for 4 Weeks

HBV DNA



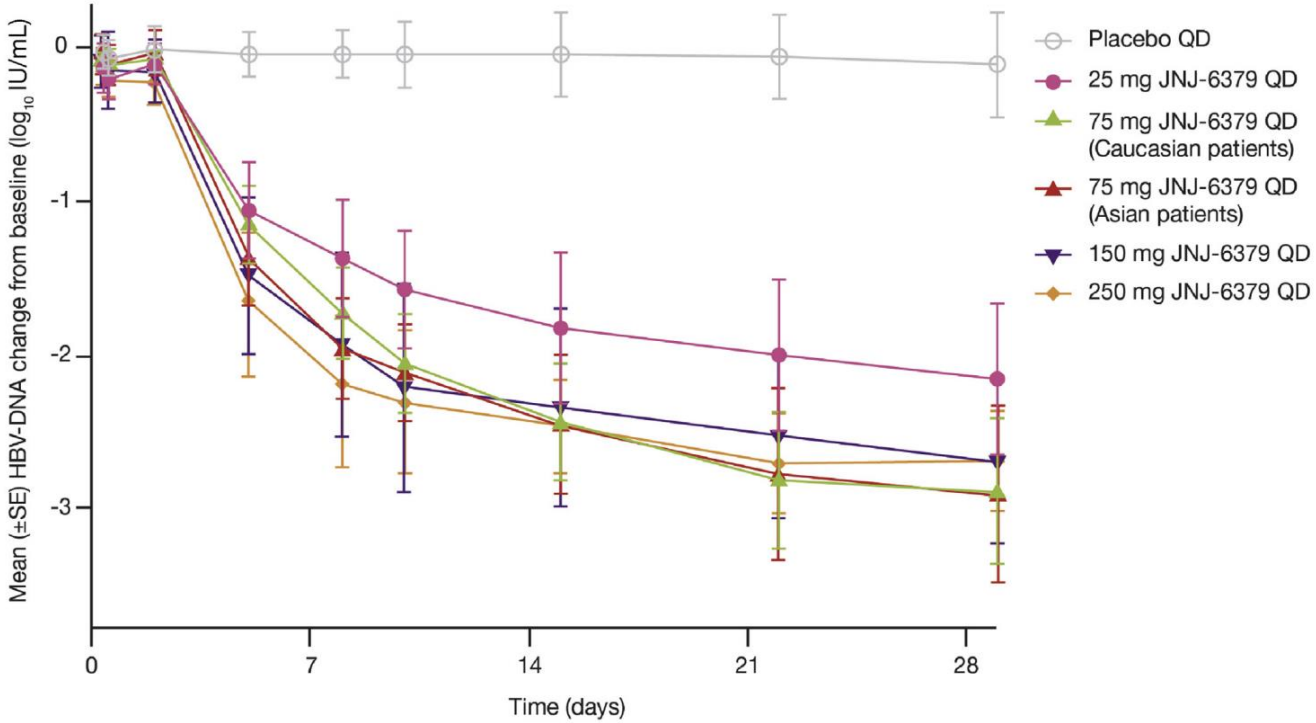
HBV RNA



Yuen MF et al. *Lancet Gastroenterol Hepatol*. 2020:5:152-66.

1st/2nd Generation: JNJ-5616379 (Bersacapavir) for 4 Weeks

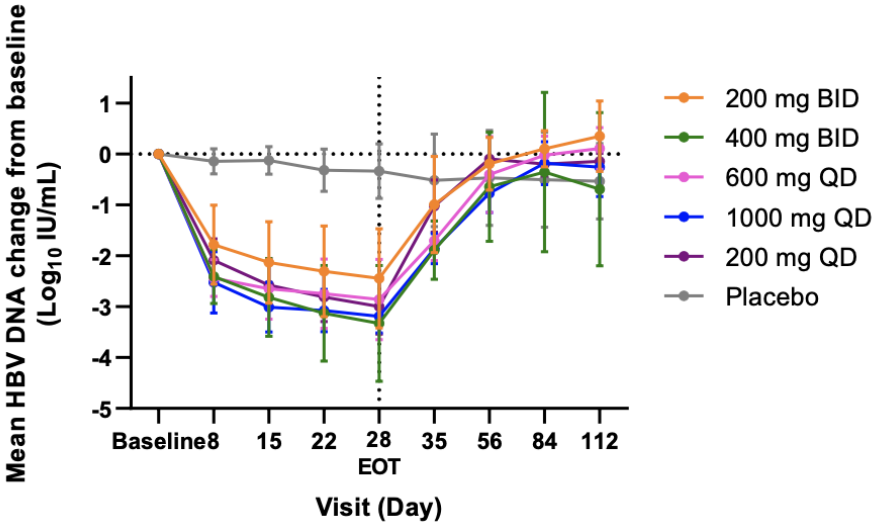
HBV DNA



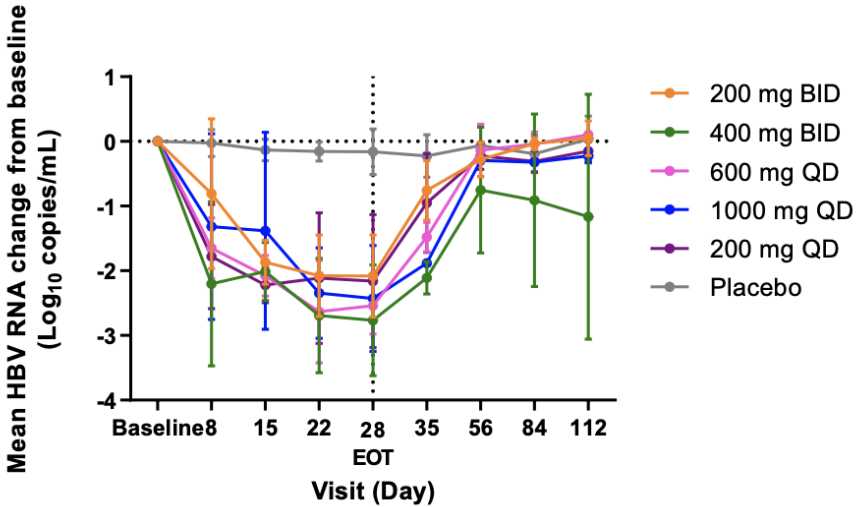
Zoulim F et al. *Gastroenterology*. 2020;159:521-33.

3rd Generation: RO7049389 (Linvencorvir) for 4 Weeks

HBV DNA



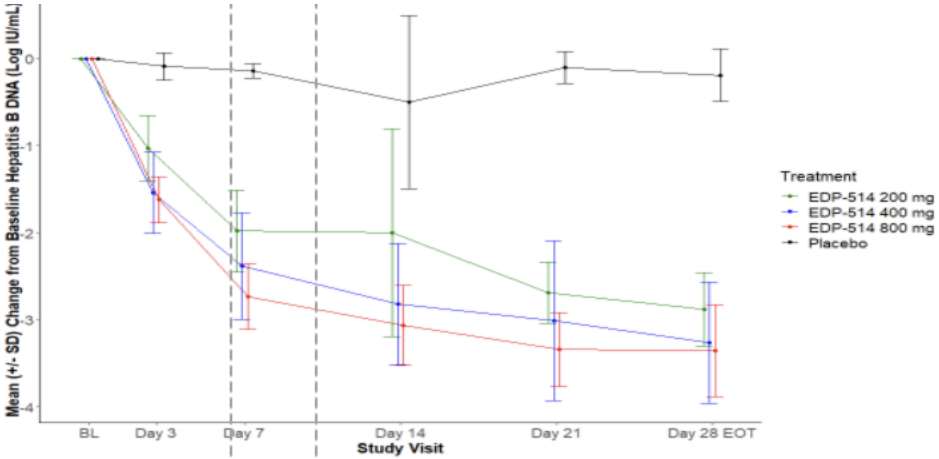
HBV RNA



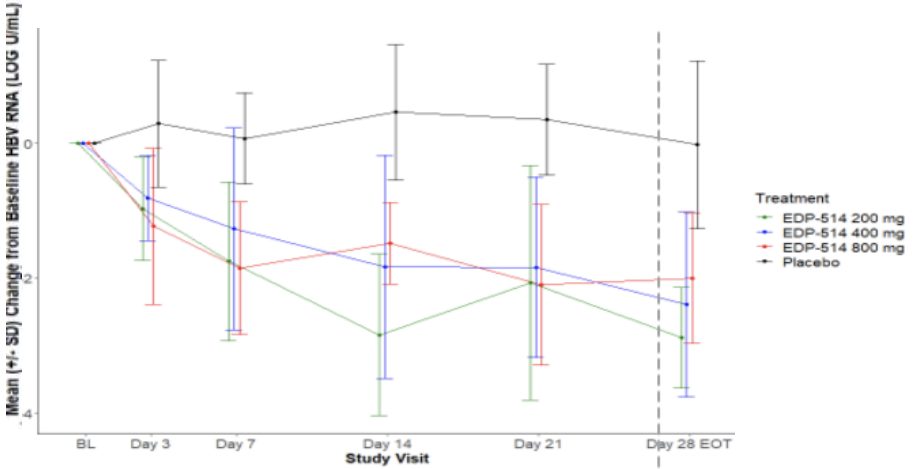
Yuen MF et al. *Lancet Gastroenterol Hepatol*. 2021;6:723-32.

4th Generation: EDP-514 for 4 Weeks

HBV DNA

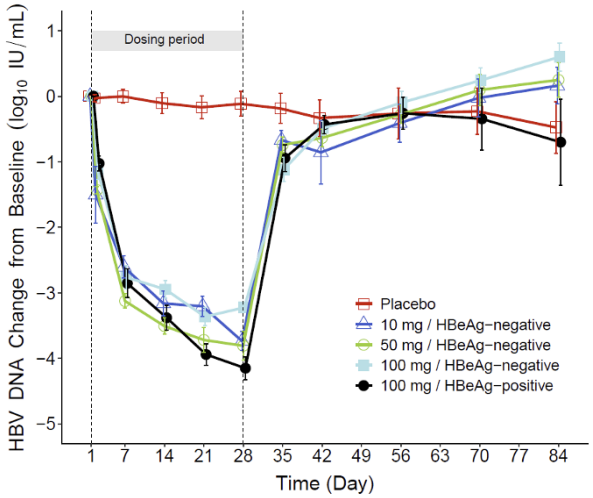


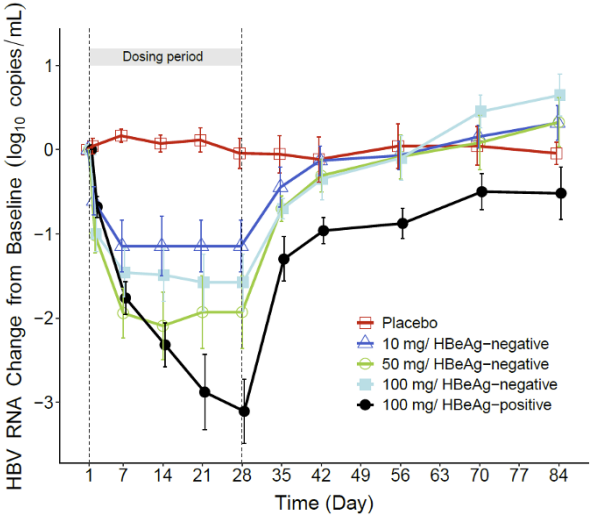
HBV RNA



Yuen MF et al. EASL. 2022. Abs 1511.

4th Generation: ALG-000184 for 4 Weeks





HBeAg negative

HBV DNA reduction (log)
10 mg: 3.7 IU/mL
50 mg: 3.8 IU/mL
100 mg: 3.2 IU/mL

HBV RNA reduction (log)
10 mg: 1.2 copies/mL
50 mg: 1.9 copies/mL
100 mg: 1.6 copies/mL

HBeAg positive (100 mg)

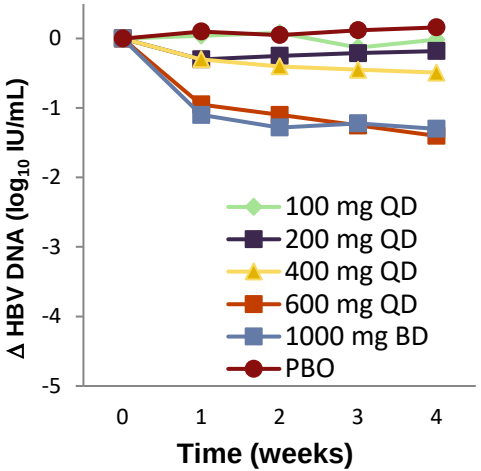
HBV DNA reduction (log): 4.2 log IU/mL
HBV RNA reduction (log): 3.1 copies/mL

Yuen MF et al. *ILC*. 2022. SAT365.

Development of More Potent (1st → 4th) CpAMs

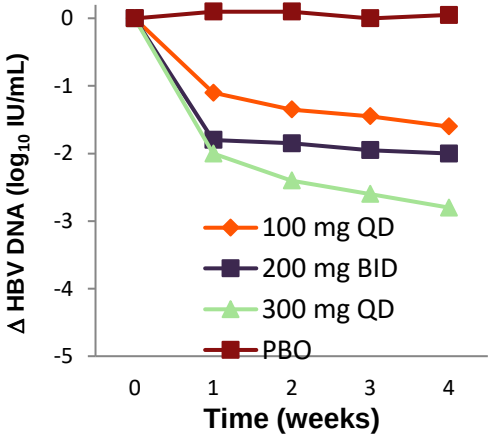
Next Gen CpAMs achieve greater HBV DNA suppression in vivo

1. NVR3-778



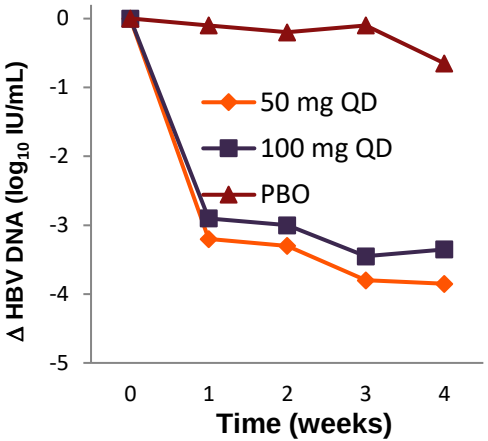
2000 mg⇨ 1.4 log reduction

2. ABI-H0731



300 mg⇨ 2.7 log reduction

3. ALG-000184

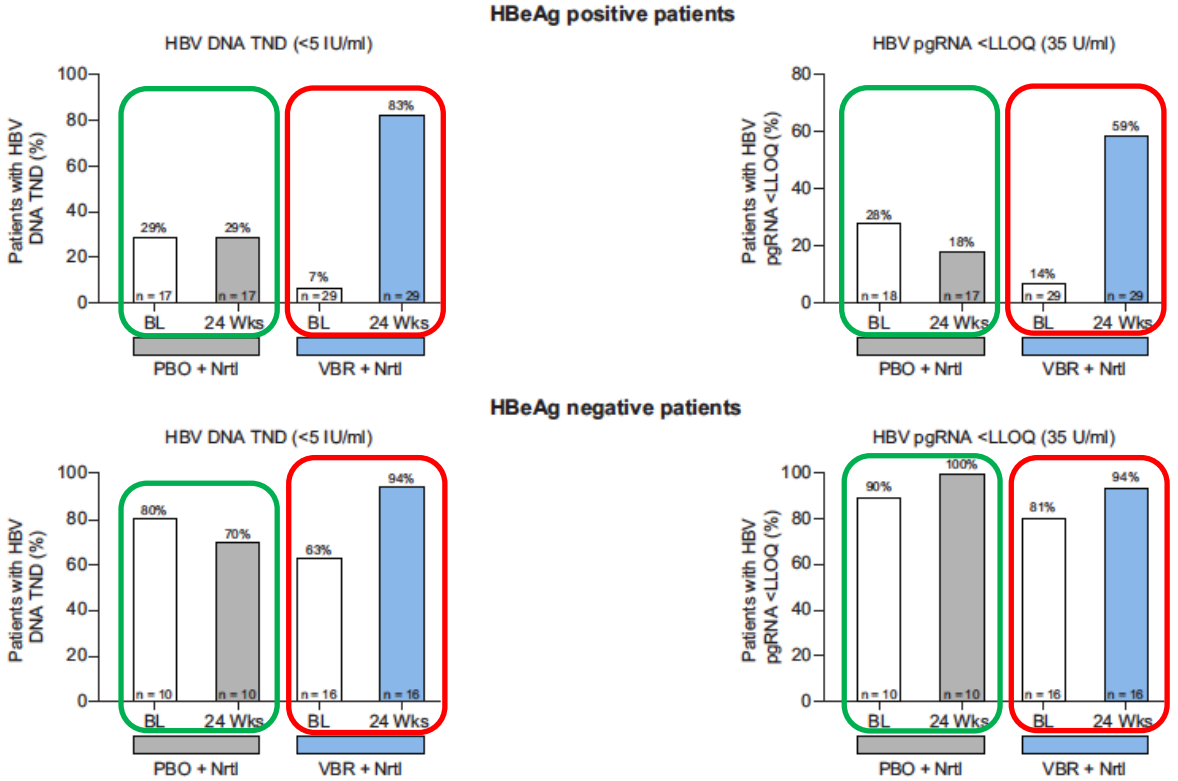


50 mg⇨ 3.8 log reduction

Yuen MF et al. *Gastroenterol*. 2019;156:1392–1403; Yuen MF et al. *Lancet Gastroenterol Hepatol*. 2019;5:152-66; Gane E et al. *Hepatology*. 2021;74:516A.

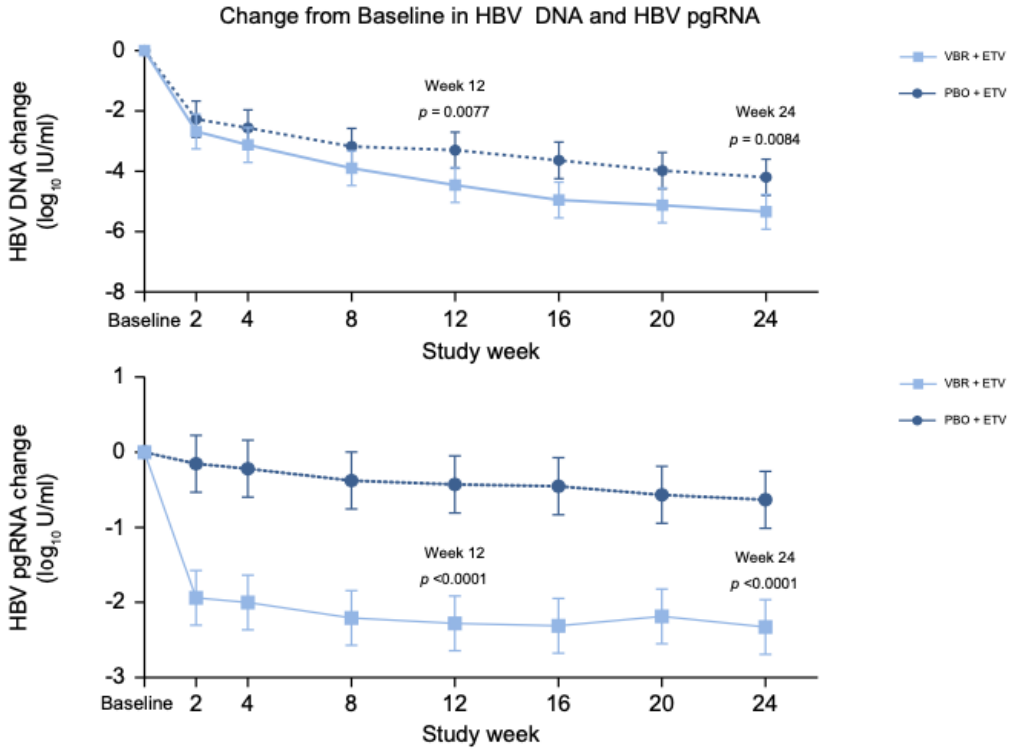
24 – 48 Weeks Treatment with CpAMs

Vebicorvir: 24 weeks in NUC-Treated Patients (HBeAg +/-)



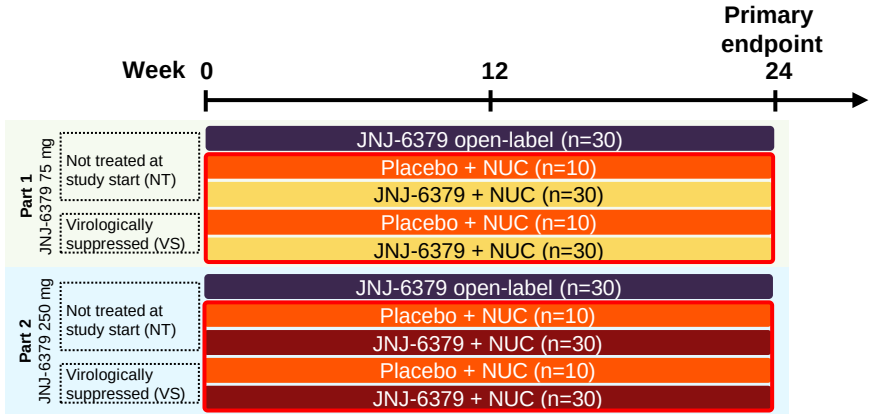
Yuen MF et al. *J Hepatol*. 2022;77:642-52.

Vebicorvir: 24 Weeks in Treatment-Naïve HBeAg +ve Patients



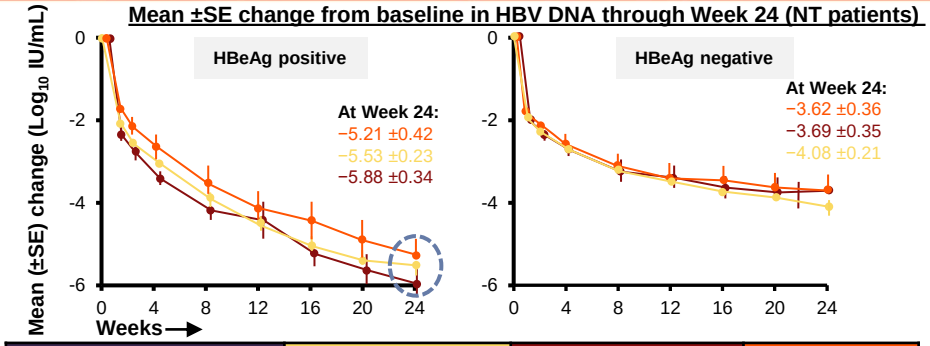
Sulkowski MS, Yuen MF. *J Hepatol*. 2022;77:1265-75.

JNJ-56136379 (Bersacapavir): 24 Weeks



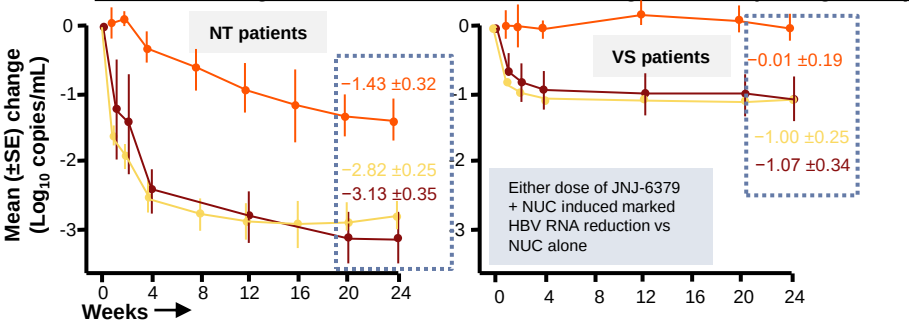
[a]JNJ-6379 treatment could be extended to 48 weeks if response criteria were met. Red boxes above indicate this presentation focused on placebo and JNJ-6379 arms only

Mean ±SE change from baseline in HBV DNA through Week 24 (NT patients)



HBV DNA <LLOQ at Wk 24, n (%)	JNJ-6379 75 mg + NUC	JNJ-6379 250 mg + NUC	Placebo + NUC
HBeAg positive	0	4 (36)	1 (13)
HBeAg negative	14 (67)	16 (84)	12 (92)

Mean ±SE change from baseline in HBV RNA through Week 24 (HBeAg+ and -)

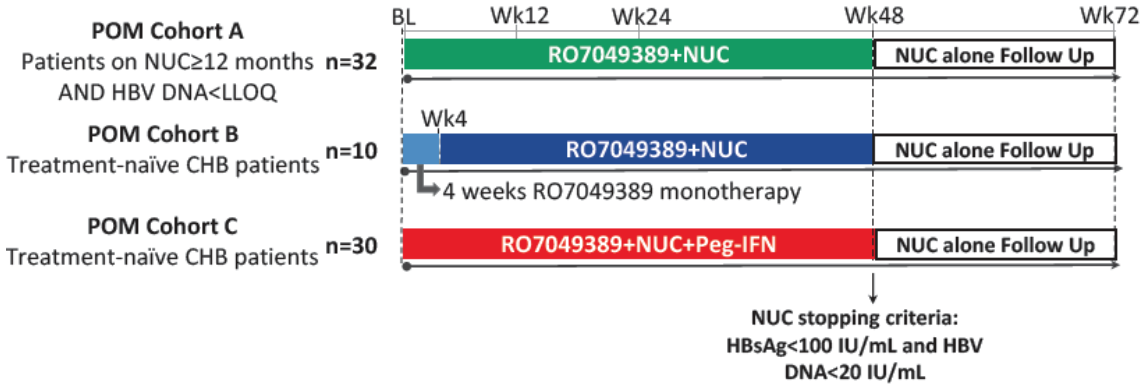


HBV RNA TND, n (%)	JNJ-6379 75 mg + NUC	JNJ-6379 250 mg + NUC	Placebo + NUC
BL	2 (7)	3 (11)	3 (14)
Week 24	16 (59)	19 (76)	9 (45)

HBV RNA TND, n (%)	JNJ-6379 75 mg + NUC	JNJ-6379 250 mg + NUC	Placebo + NUC
BL	19 (59)	21 (72)	14 (67)
Week 24	13 (100)	8 (100)	1 (14)

Janssen H et al. *EASL*. dILC2020. #LBP12.

RO-7049389 (Linvencorvir) +/- IFN in NUC-Treated & Treatment-Naïve Patients: 48 Weeks



HBV DNA

RO7049389 in combination with standard of care (SoC) demonstrated potent HBV DNA suppression even in HBeAg positive high viral load (HVL) patients

- In Cohort A, mean HBV DNA levels of the NUC-suppressed patients remained <LLOQ during the study
- In Cohort B, 100% (10/10) patients achieved HBV DNA <LLOQ at Week 48:
  - 100% (2/2) patients with HVL achieved HBV DNA <LLOQ
  - All NUC-compliant patients sustained HBV DNA <LLOQ during NUC-alone follow-up
- In Cohort C, 86% (24/28) patients who completed 48-week study treatment achieved HBV DNA <LLOQ by Week 48
  - 78% (14/18) patients with HVL achieved HBV DNA <LLOQ, and 94% (17/18) achieved HBV DNA <50 IU/mL

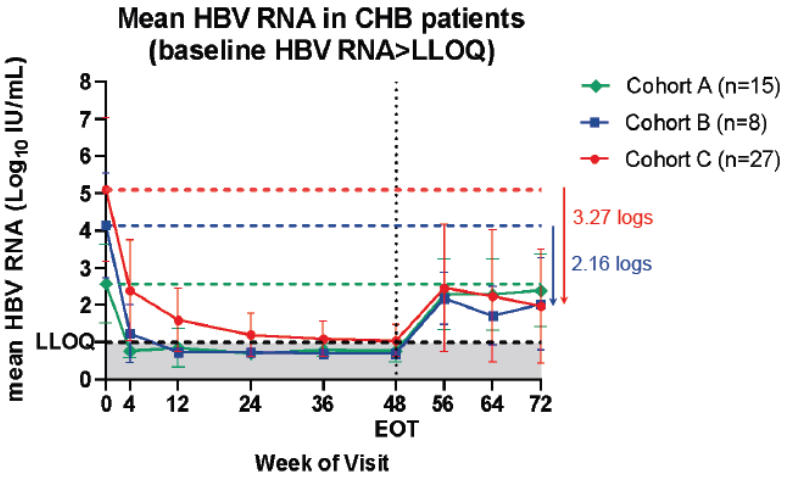
Yuen MF et al. *EASL*. 2022. SAT427.

RO-7049389 (Linvencorvir) +/- IFN in NA-Treated and Treatment-Naïve Patients: 48 Weeks

HBV DNA

Retained HBV RNA reduction from baseline in treatment-naïve patients after the cessation of RO7049389 may suggest a certain level of suppression in cccDNA level/transcriptional activity

- In NUC-suppressed patients in Cohort A, 93.3% (14/15) patients* achieved HBV RNA <LLOQ at Week 48 but rebounded to approximately the baseline levels in the NUC-alone follow-up.



In the treatment-naïve patients in Cohort B and C,

- 100% (8/8) and 88% (22/25) patients* achieved HBV RNA <LLOQ at Week 48, respectively.
- An average of at least 2 logs reduction from baseline was retained after the cessation of RO7049389 for 24 weeks.
- 28.6% (2/7) and 44% (11/25) patients* had HBV RNA <LLOQ at Week 72, respectively.

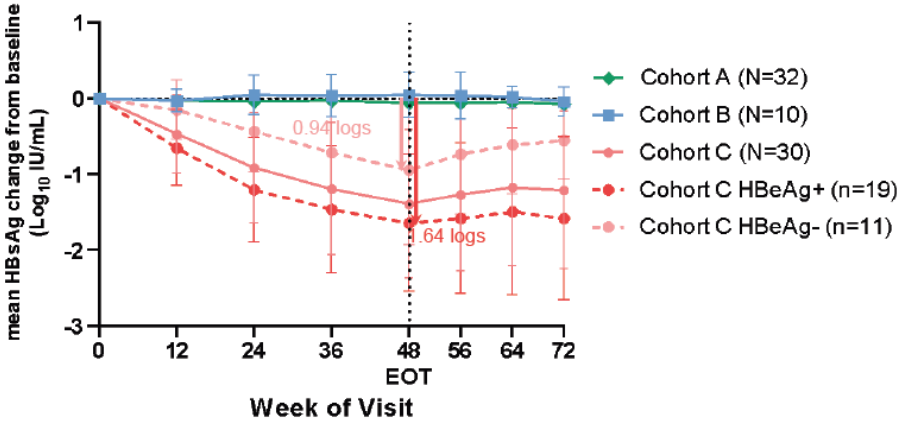
Yuen MF et al. *EASL*. 2022. SAT427.

RO-7049389 (Linvencorvir) +/- IFN in NUC-Treated & Treatment-Naïve Patients: 48 Weeks

HBsAg

- In NUC-suppressed patients in Cohort A, no obvious HBsAg declines were observed during the study.
- In treatment-naïve patients in Cohort B and C, no HBsAg loss was observed.
  - With CpAM+NUC treatment, limited effect on HBsAg levels. Only 2 out of 10 patients had maximal HBsAg decline by 0.4-0.45 logs, and both occurring after Grade 3 ALT flares.
  - With CpAM+NUC+Peg-IFN treatment, effect on HBsAg levels at Week 48:
    - Mean HBsAg decline was 1.39 logs with baseline (BL) mean level of 3.96 log.
    - HBeAg+ patients had average 1.64 logs decline and generally sustained during post-treatment period.
    - Patients with BL HBsAg ≥4 log achieved mean HBsAg decline by 1.72 logs vs 0.95 logs in BL HBsAg <4 log.

Mean HBsAg change from baseline over 72 weeks



Hou JL et al. *EASL*. 2022. THU408.

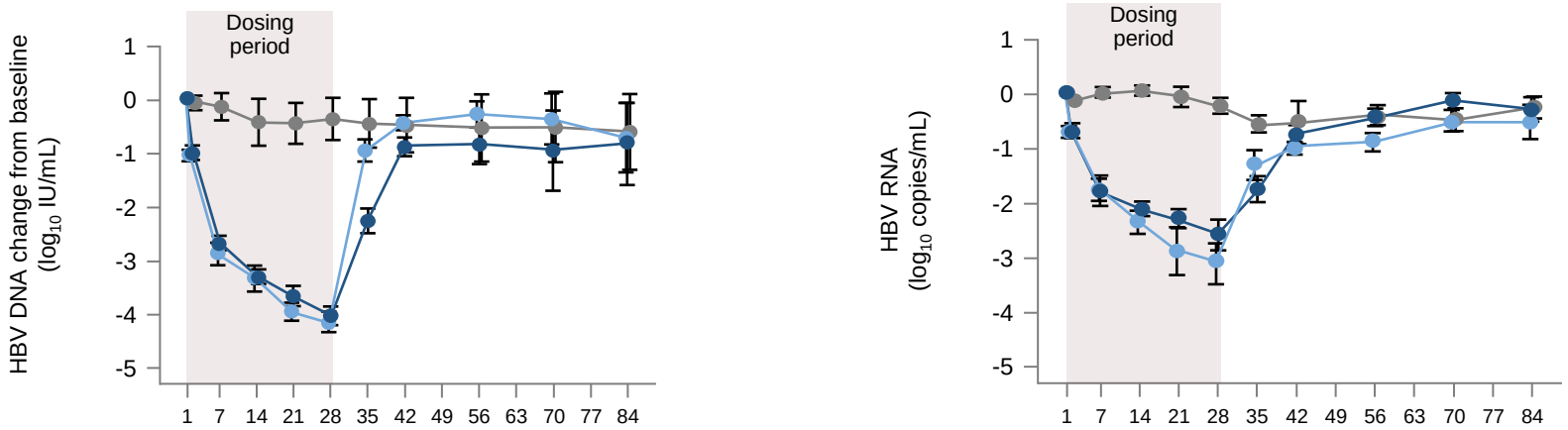
ALG-000184: Early Promising Results on HBV DNA/HBV RNA in HBeAg +ve Patients

Antiviral activity: HBV DNA and HBV RNA

HBeAg-positive CHB patients dosed with 100 mg and 300 mg ALG-000184 had similar rapid and profound declines in HBV DNA/RNA at Day 28:

- HBV DNA mean decline: 4.2 (100 mg), 4.0 log10 IU/mL (300 mg)
- HBV RNA mean decline: 3.1 (100 mg), 2.6 log10 copies/mL (300 mg)

Mean (SEM) change from baseline in HBV DNA and RNA



Hou JL et al. *EASL*. 2022. Poster #1329.

ALG-000184: Early Promising Results on HBsAg Levels in HBeAg +ve Patients

Antiviral activity: HBsAg

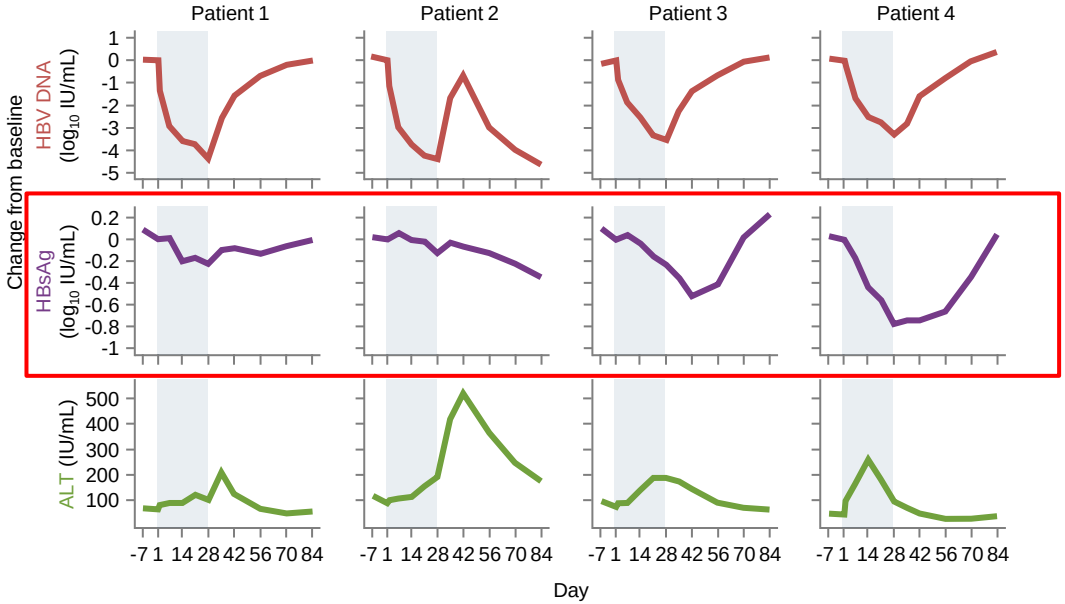
- 3/7 patients dosed with 300 mg experienced reduction in HBsAg (0.23–0.78 $\log_{10}$ IU/mL)
- 1 patient (100 mg cohort) with high exposures of ALG-001075 equivalent to 300 mg had 0.5 $\log_{10}$ IU/mL decline in HBsAg

Patients with HBsAg decline in the 100 mg and 300 mg cohorts

Patient[a]	Dose (mg)	HBsAg baseline ($\log_{10}$ IU/mL)	Max HBsAg decline ($\log_{10}$ IU/mL)
1	300	3.66	-0.23
2	300	4.82	-0.35
3	100	4.80	-0.52
4	300	4.27	-0.78

[a]Among the 12 patients enrolled in the 300 mg dose cohort, only 7 were evaluable; 2 patients had missing laboratory data due to prolonged COVID lockdown in China, 2 patients were randomized to placebo and 1 patient had HBsAg levels above the upper limit of assay sensitivity throughout the study

Individual HBV DNA, HBsAg, and ALT profiles of 4 patients with HBsAg declines



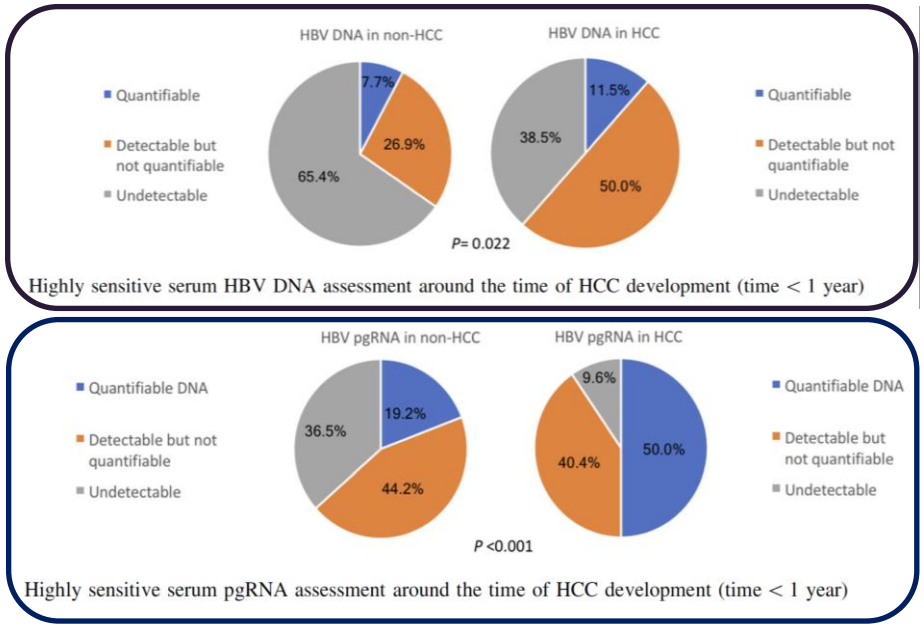
Hou JL et al. *EASL*. 2022. Poster #1329.

Emerging Concepts of CpAMs

- Any potential benefits of better HBV DNA and additional HCV RNA suppression on top of NUCs?
- Any concern on development of viral resistance if given as monotherapy?
- Any action on cccDNA?
- Any safety concern on long-term treatment?

CpAM- Further HBV DNA/RNA Suppressions Decrease HCC?

Residual HBV DNA and pgRNA viraemia is associated with hepatocellular carcinoma in chronic hepatitis B patients on antiviral therapy



Highly sensitive serum HBV DNA assessment around the time of HCC development (time < 1 year)

Highly sensitive serum pgRNA assessment around the time of HCC development (time < 1 year)

Additional HBV DNA and HBV RNA by CpAM on NUC-treated patients may further reduce HCC?

Mak LY, Yuen MF. *J Gasttoenterol*. 2021;56:479-488.

CpAM - Further HBV DNA/RNA Suppression Decrease HBV DNA Integration?

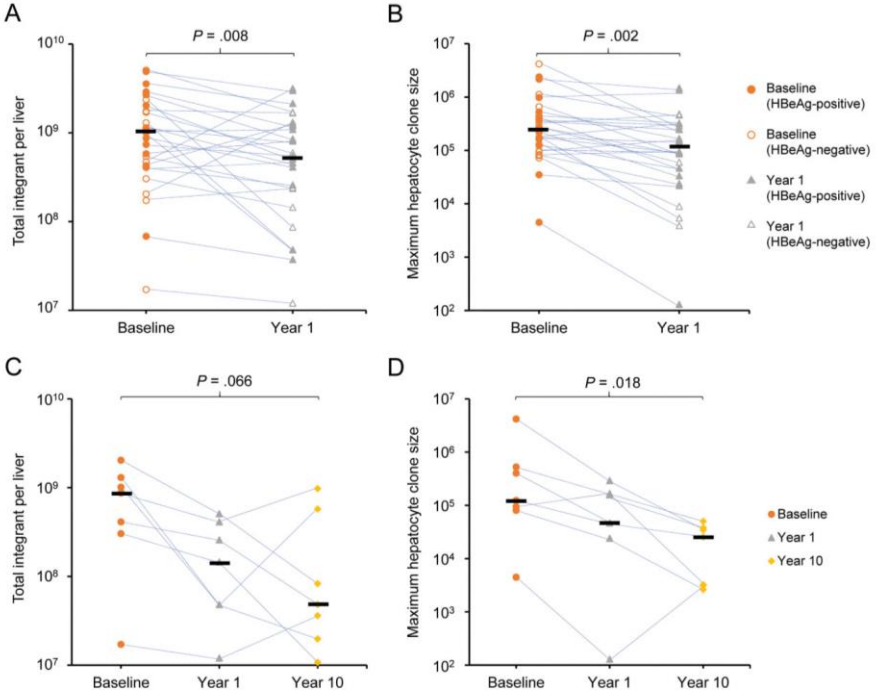


Figure 3. HBV DNA integration (*A* and *C*) and maximum hepatocyte clone size (*B* and *D*) before and after NUC treatment. Degree of HBV DNA integration and maximum hepatocyte clone size of the 28 patients with baseline and year 1 liver biopsies (*A* and *B*) and the 7 patients with 3 liver biopsies at baseline, year 1 and year 10 (*C* and *D*) are shown. Abbreviations: HBV, hepatitis B virus; NCU, nucleos(t)ide analogue.

Additional HBV DNA by CpAM on NUC-treated patients may further reduce HBV integration?

Chow N, Yuen MF. *Clin Infect Dis*. 2023;76:e801-e809.

1st/2nd Generation CpAM Monotherapy – Viral Resistance

Viral breakthroughs

- No viral breakthroughs (VBT) in the JNJ-6379 + NUC combination arms
- Confirmed viral breakthrough in 5/28 patients on JNJ-6379 75 mg monotherapy
  - Associated w/T33N RAS
- One patient on JNJ-6379 250mg monotherapy with non-response (<1 Log_{10} IU/mL decline from baseline at Week 4) had subsequent VBT

CAM resistant strain: T33N

- 85 fold change in EC50
- Viral population in those with VBT: 96.7 – 99.7%
- Patients with VBT switched to NA rescue treatment or added with NA treatment, all had HBV DNA declines

Verbinnen T et al. EASL. dILC2020. # 856; Janssen H et al. *EASL*. dILC2020. #LBP12.

Decreasing Chance of Viral Resistance in More Potent Antiviral Agents

More profound HBV DNA suppression e.g. Tenofovir/ Entecavir associated with minimal resistance (compared to first/ second generation of NUCs)

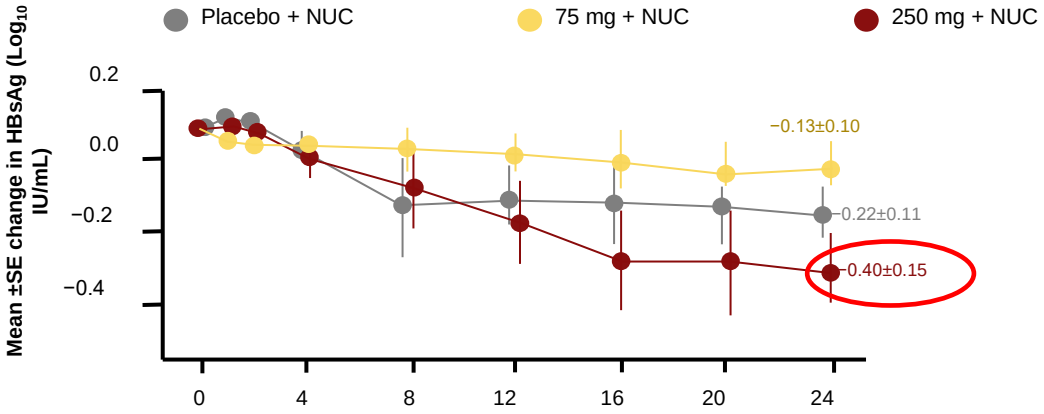
- HBV DNA suppression of NUCs vs. CpAM
- Mean HBV DNA reduction at 4 weeks of antiviral treatment
- TAF: 2.81 log IU/mL[1]
- Entecavir: 2.81 log IU/mL[2]
- Aligo 000184: 4.0 log IU/mL[3]

More potent CpAM given as monotherapy overcome emergence of viral resistance?

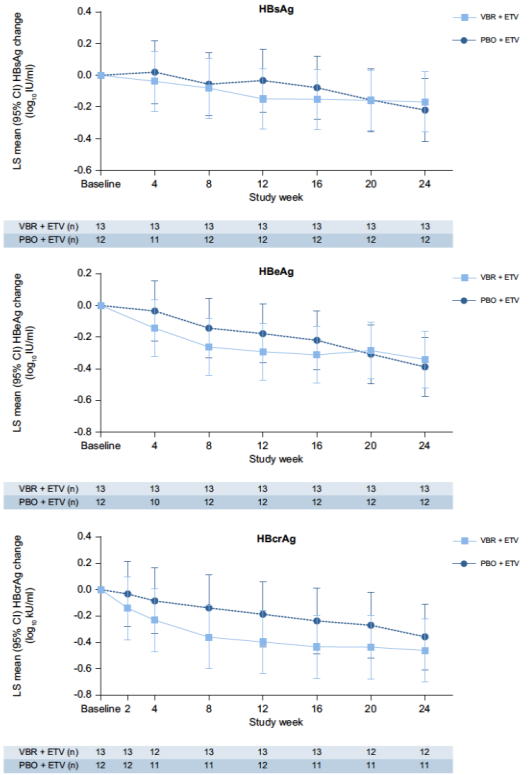
1. Agarwal K et al. *J Hepatol*. 2015;62:533-540; 2. de Man RA et al. *Hepatology*. 2001;34:578-582; 3. Hou JL et al. *AASLD*. 2022. Poster #1329.

CpAM (1st/2nd Generation) (24 Weeks) On cccDNA Activity?

HBeAg +ve Rx naïve patients receiving Bersacapavir



HBeAg +ve Rx naïve patients receiving Vebicorvir



Janssen H, et al. *EASL*. dILC2020. #LBP12; Sulkowski MS, Yuen MF. *J Hepatol*. 2022;77:1265-75.

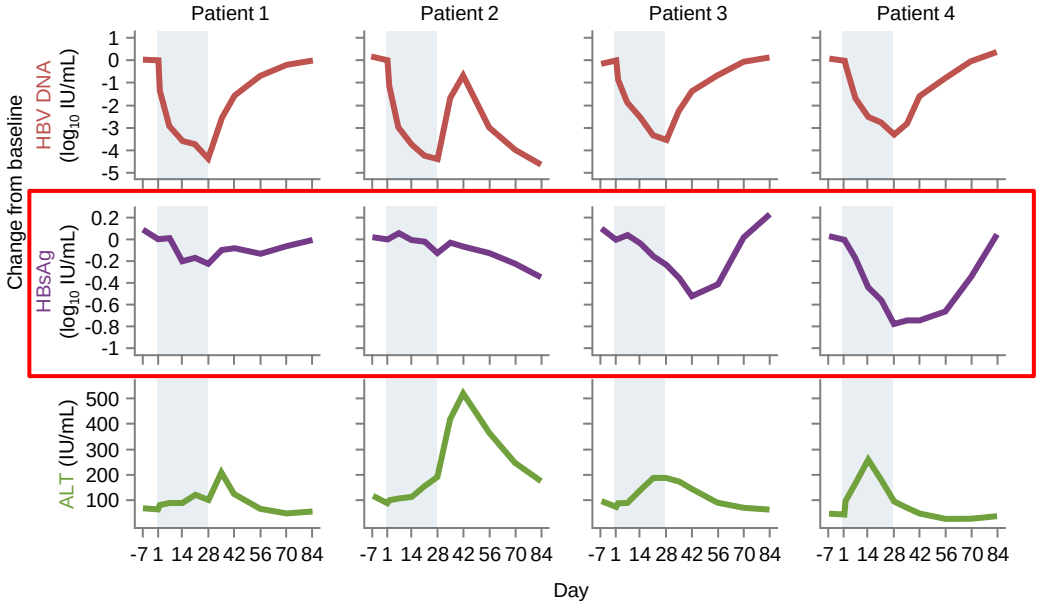
CpAM (4th Generation) On cccDNA Activity?

Patients receiving ALG000184: HBsAg decline in the 100 mg and 300 mg cohorts

Patient[a]	Dose (mg)	HBsAg baseline (log_{10} IU/mL)	Max HBsAg decline (log_{10} IU/mL)
1	300	3.66	-0.23
2	300	4.82	-0.35
3	100	4.80	-0.52
4	300	4.27	-0.78

[a]Among the 12 patients enrolled in the 300 mg dose cohort, only 7 were evaluable; 2 patients had missing laboratory data due to prolonged COVID lockdown in China, 2 patients were randomized to placebo and 1 patient had HBsAg levels above the upper limit of assay sensitivity throughout the study

Individual HBV DNA, HBsAg, and ALT profiles of 4 patients with HBsAg declines



Hou JL et al. *AASLD*. 2022. Poster #1329.

Conclusions

- All CpAMs were associated with HBV DNA and HBV RNA reduction: primary mode of action confirmed
- Early generation CpAMs showed modest effects on HBsAg (also HBeAg/ HBcrAg) when given for 24 weeks in HBeAg +ve treatment naïve patients
- Latest generation CpAM
  - Showed more profound HBV DNA and HBV RNA suppression
  - Showed initial promising HBsAg reduction even given for 4 weeks only
- Future explorations for CpAM:
  - HBsAg effects of longer treatment duration of more potent CpAM – Functional cure?
  - Further reduction of HCC and HBV DNA integration when added to NUC?
  - Potential for monotherapy?

Thank You

Questions?

- **Live:** Please utilize the microphones in the middle of the ballroom or write your question on the Q&A cards in front of you.
- **Virtual:** Please submit your questions via the Q&A section of the livestream viewer.