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HBV/HDV-ACT Connect
(ADVANCING CURATIVE TREATMENTS)

HBV Overview of the Last 3 Years For Drug Development: Phase 2 Trials

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Disclosures

- Consulting: Aligos, Arbutus, Arrowhead, Galmed, Gilead, GSK, Intercept, Janssen, Merk, Roche, Takeda
- Data Monitoring Committees: Altimmune, GSK, Takeda
- Research funding: Assembly Biosciences, Bristol-Myers Squibb, Eiger, Eli Lily, Enanta, Gilead, GSK, Intercept, Janssen, Merck, Mirum, Novo Nordisk

Why Aim for Functional Cure HBV Infection?

Potential advantages of clearing HBsAg versus long term suppressive therapy

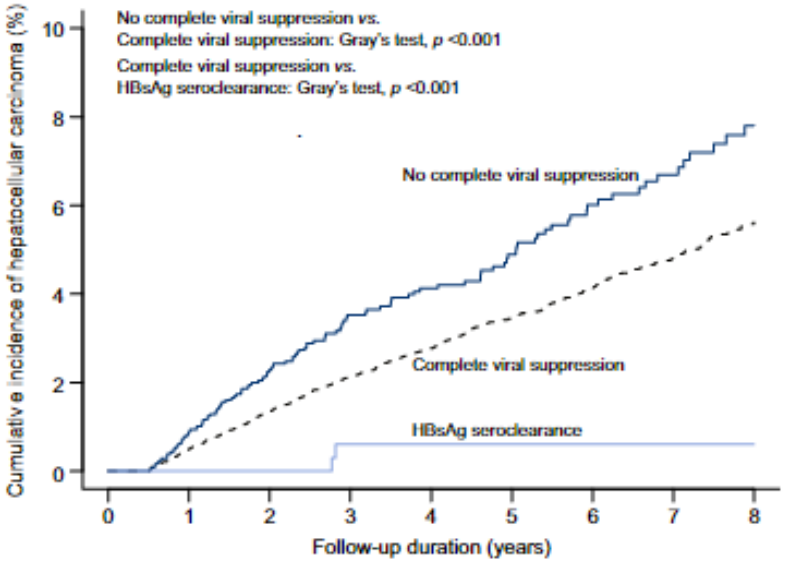
- **Avoid risks of long term NA toxicity**
- **Reduce costs associated with long term/lifelong therapy**
- **Avoid risks of hepatitis flare with discontinuation of therapy**
- **Reduce risk of reactivation years after treatment stopped (e.g. w/chemo)**

Improve clinical outcomes

Impact of HBsAg Seroclearance on Nucleotides on Long Term Outcomes

20,263 CHB patients on NA therapy

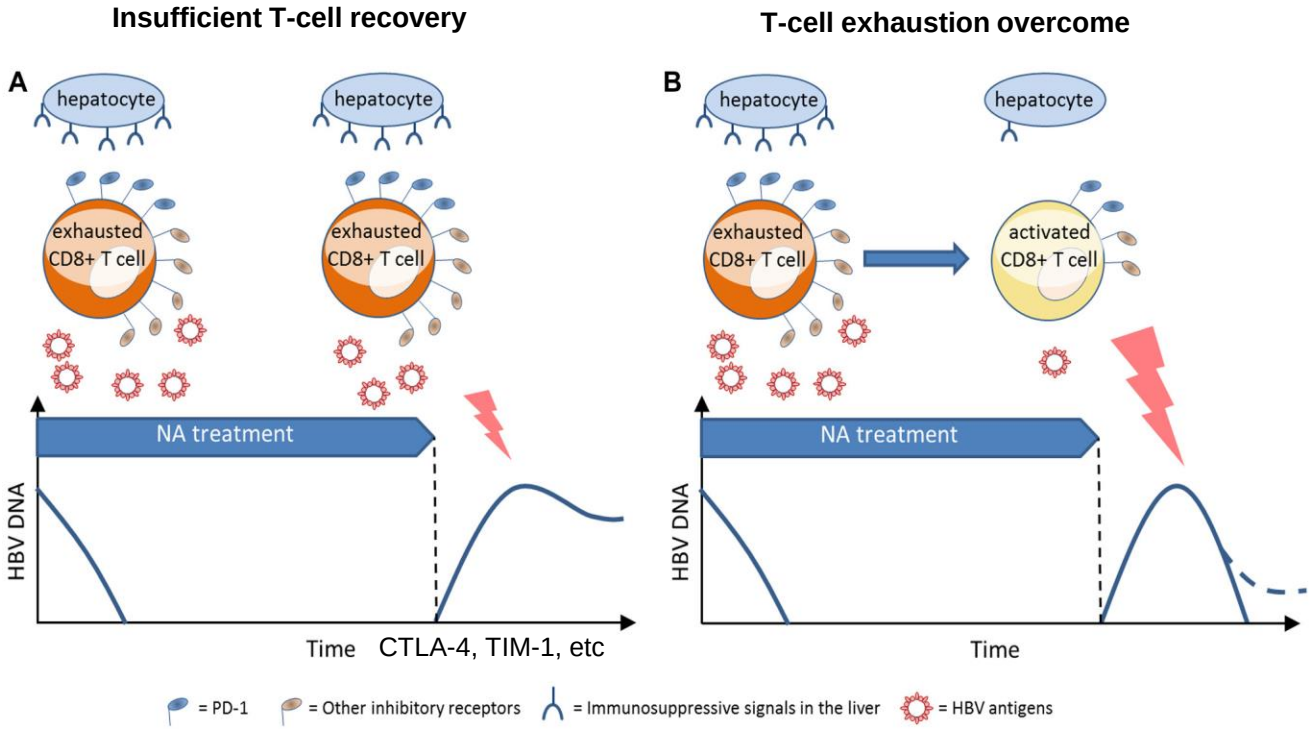
Cumulative incidence of HCC (%)



HBsAg clearance associated with lower risk of HCC

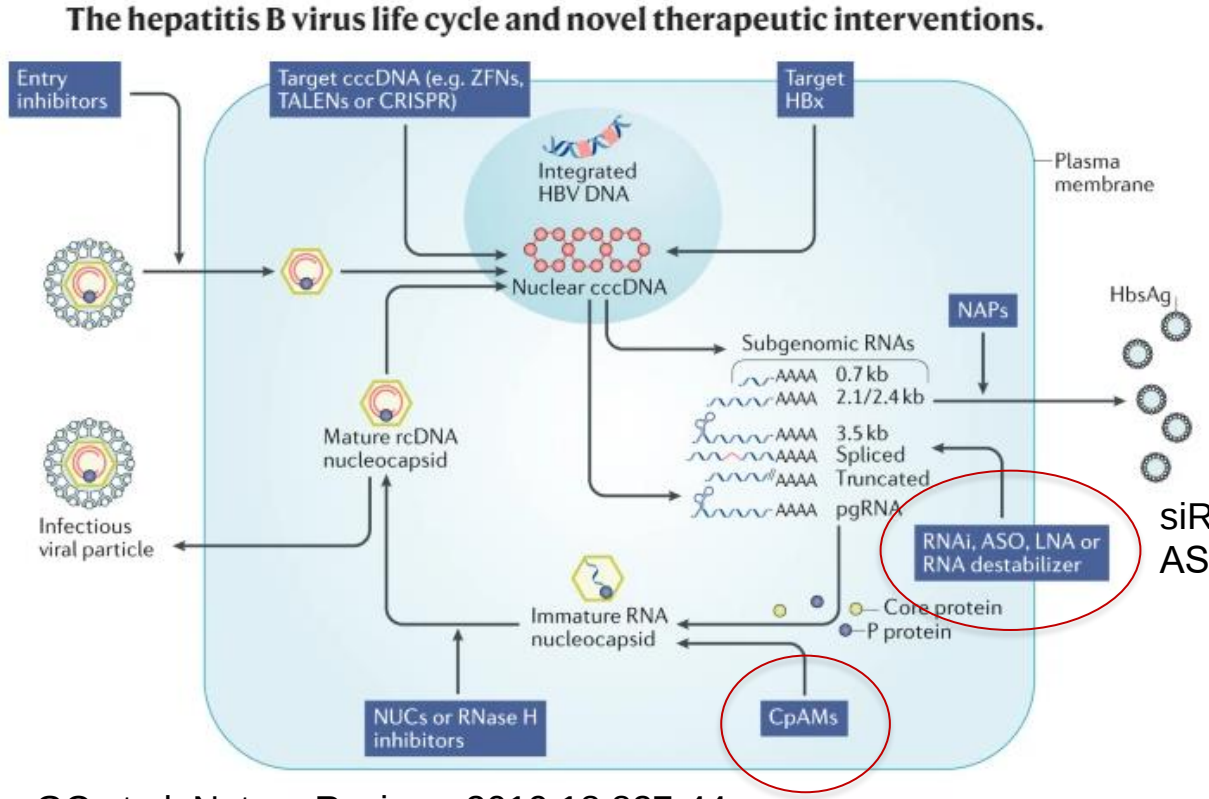
Yip TCF et al, J Hepatology 2019;70:361-370

The Concept of T-Cell Exhaustion as a Product of Chronic Antigenemia and the Potential Benefit of Immune Activation by Antigen Suppression



*The major driving hypothesis is that suppression of antigenemia (especially HBsAg) will drive T cell recovery.
Van Bommel F, Berg T. *Hepatology Communications*. 2021;5:1632-1648;

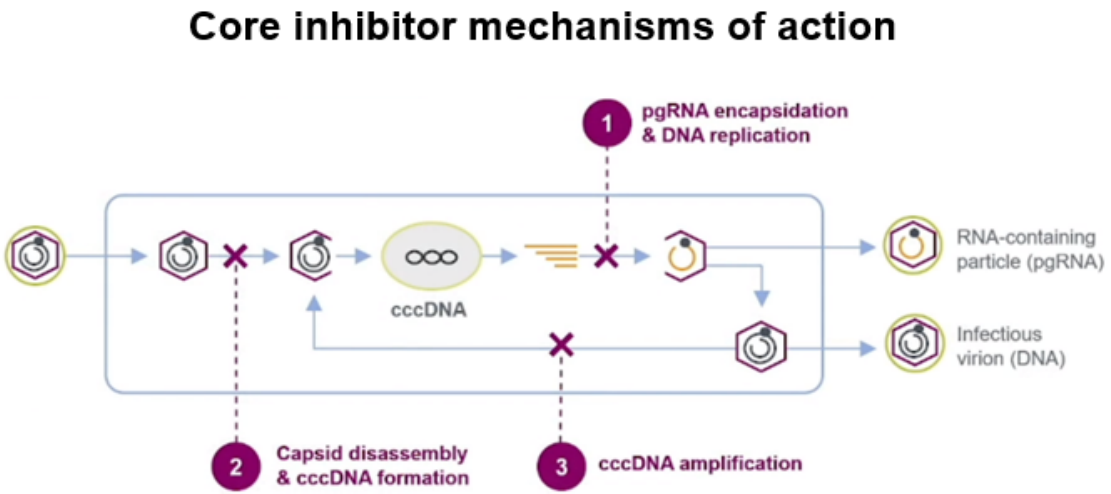
Agents Studied in Phase 2 in Past 3 Years



siRNAs
ASO's

Fanning GC et al, Nature Reviews 2019;18:827-44

Capsid Assembly Modulators (Core Inhibitors) Mechanisms of Action

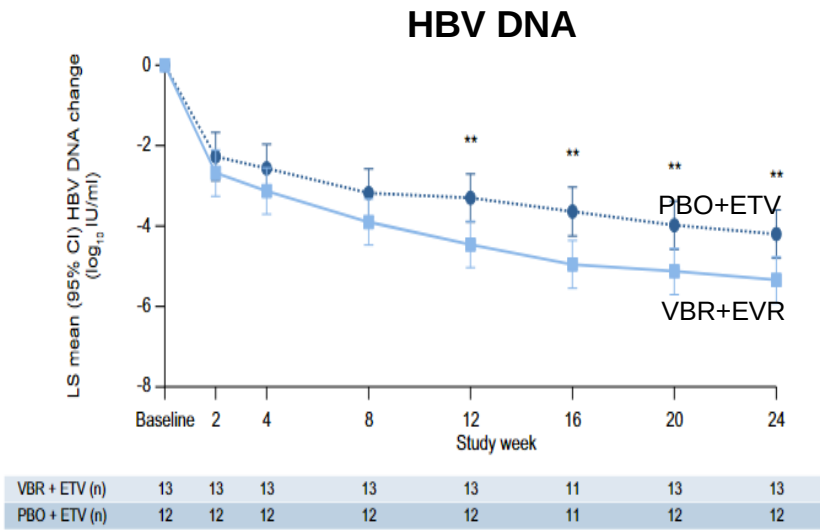


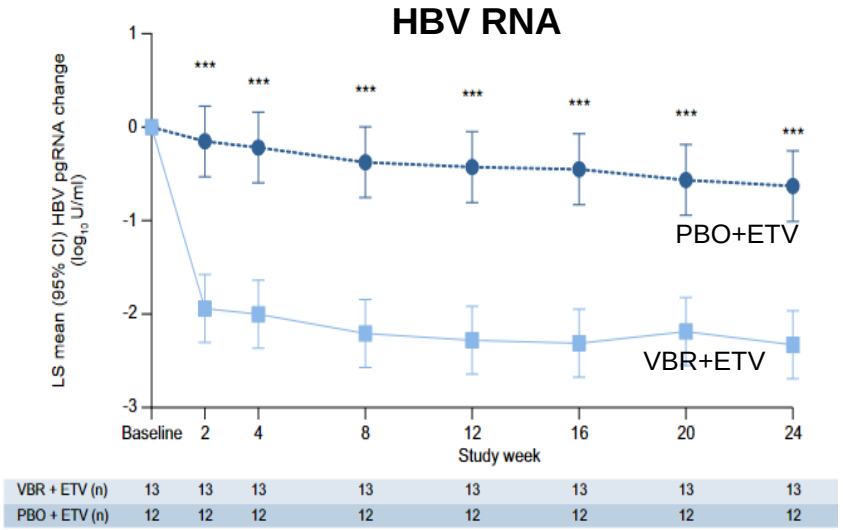
Potential therapeutic effect of core inhibitors (CAMs)

1. Prevent formation of capsids within which replication occurs
2. Core inhibitors prevent disassembly of capsids after viral entry
3. Core inhibitors inhibit facilitation by core protein of cccDNA activity

Yuen MF et al. *AASLD*. 2021; O-96.

Vebicorvir (1st Generation CAM) For Treatment-Naive Patients With CHB: Effect on HBV DNA and HBV RNA





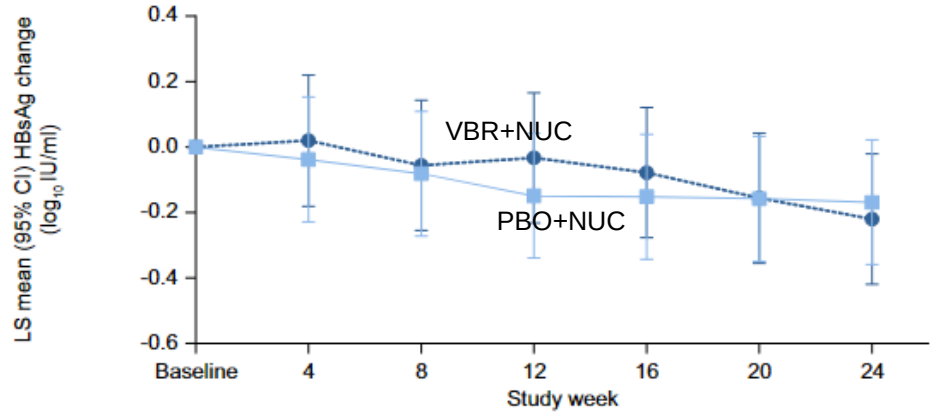
Greater HBV DNA reduction with VBR vs Placebo

Marked reduction of HBV RNA with VBR

Sulkowski MS et al. *J Hepatology*. 2022;77:1265-1275.

Vebicorvir (1st Generation CAM) For Treatment Naïve Patients With CHB: Effect on HBsAg Over 24 Weeks

HBsAg

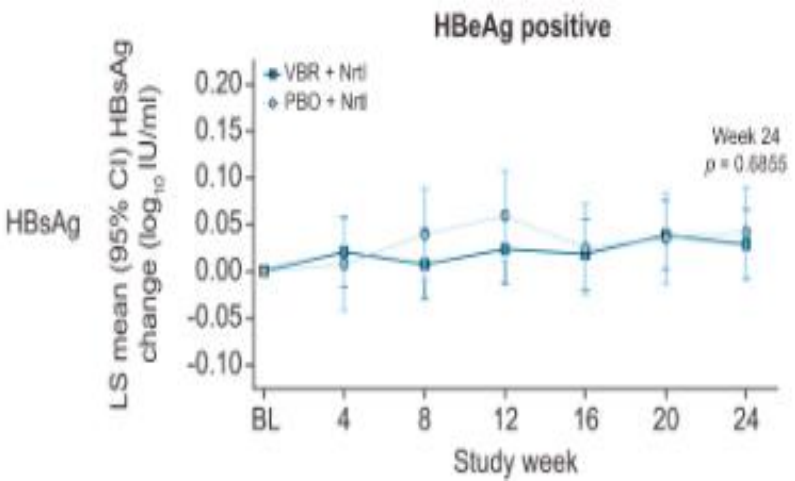


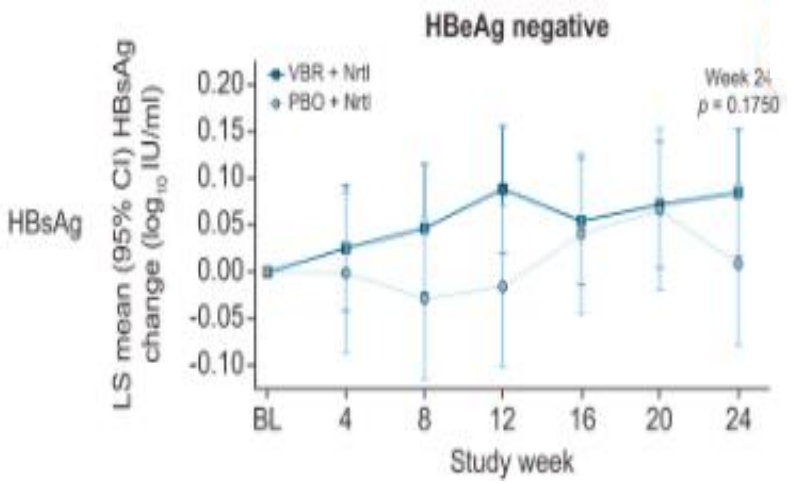
VBR + ETV (n)	13	13	13	13	13	13	13
PBO + ETV (n)	12	11	12	12	12	12	12

- No significant reduction of HBsAg with VBR vs Placebo… *nor was there at later time points*
- No patient cleared HBsAg

Sulkowski M et al. *J Hepatol*. 2022, 77, 1265–1275.

Vebicorvir (1st Generation CAM) For NUC-Suppressed Patients With CHB: Effect on HBsAg Over 24 Weeks

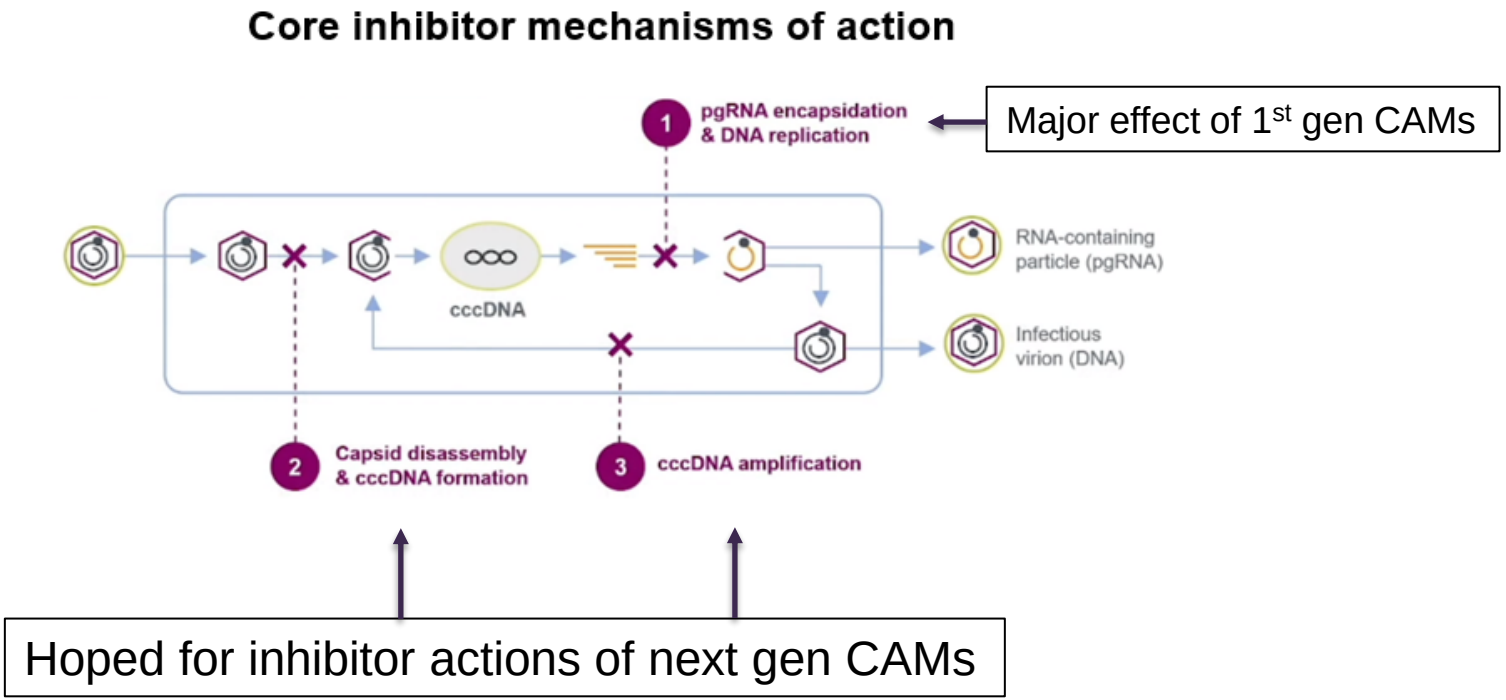




VBR had no significant effect on HBsAg

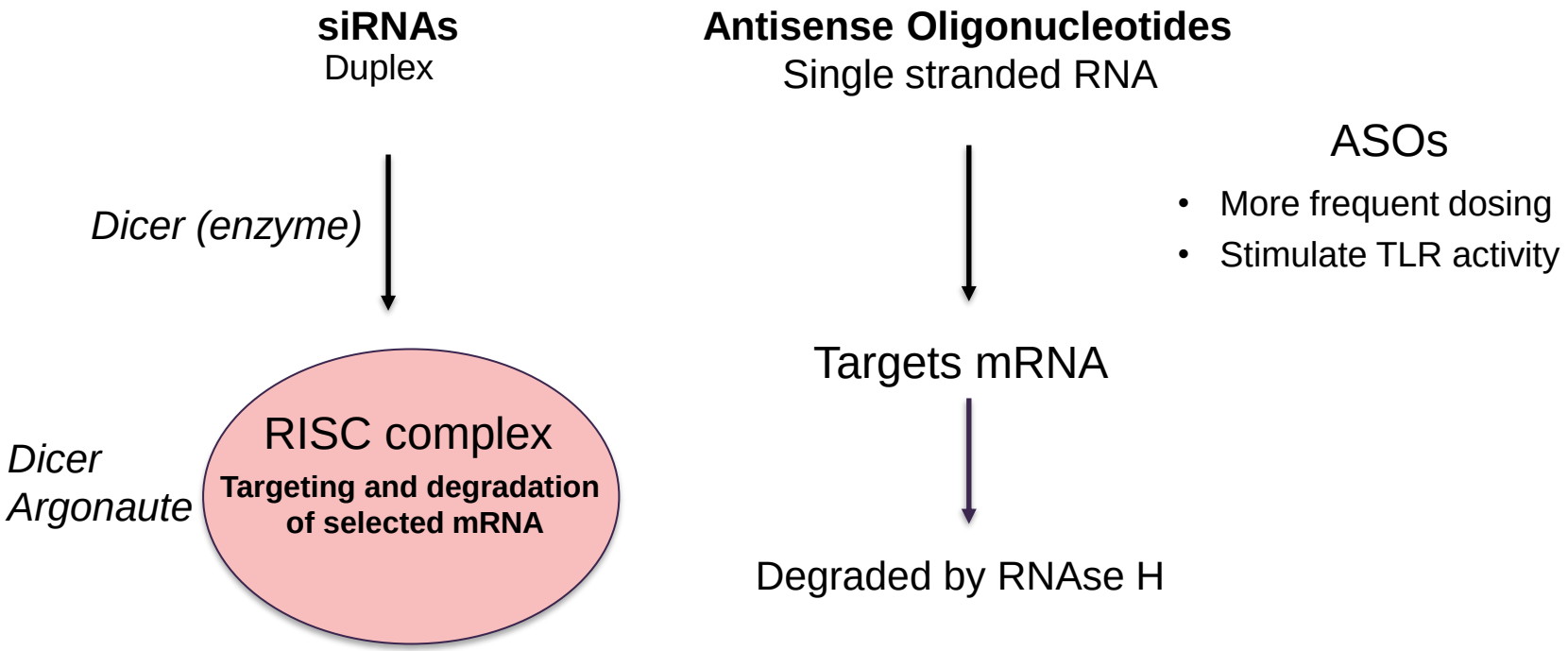
Yuen M-F et al, J Hepatol 2022;77:642-652

Capsid Assembly Modulators (Core Inhibitors): Next Generation CAMs Being Developed



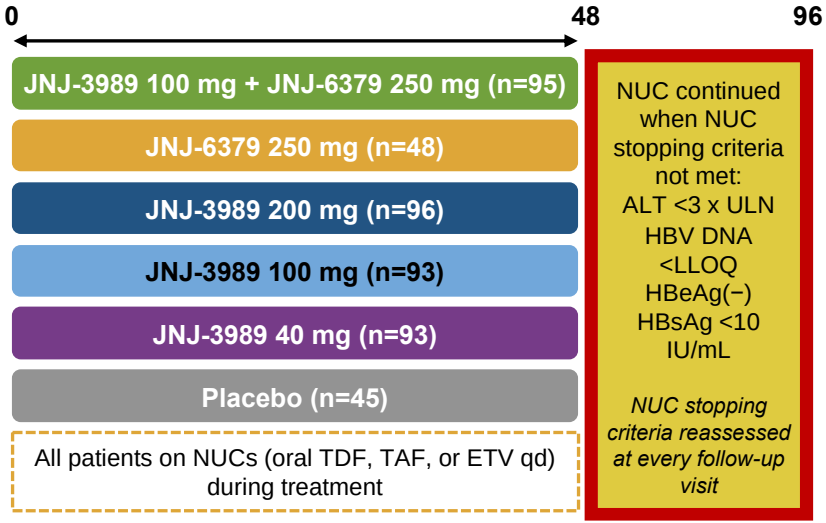
Yuen MF et al. *AASLD*. 2021; O-96.

Antisense Approaches Being Studied for HBV



Paturi S, Deshmukh MV. Front Mol Biosci 2021;8 doi.org/10.3389

Phase 2b REEF-1 Trial: Efficacy and Safety of the siRNA JNJ-3989 And/or the CAM JNJ-6379 for the Treatment of CHB



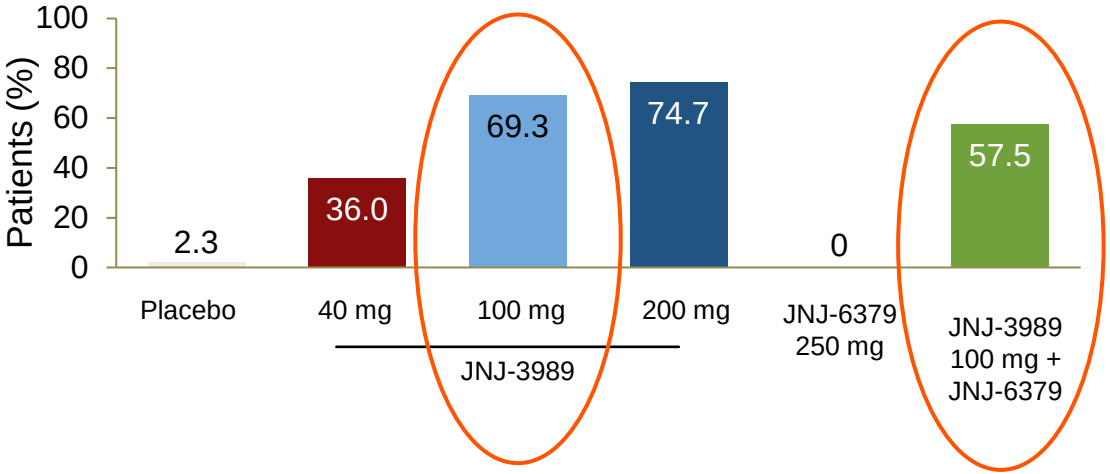
Baseline characteristics (range across arms)

- Male 56-77%
- Asian 33-46%
- Age (yrs) 42=44
- NUC-treated 62-64%
- HBeAg+ 28-32%
- HBsAg log10 IU/mL 3.6-3.8
- ALT U/L 44-66
- Liver stiffness 5.3-5.4 kpa

Yuen M-F et al. *AASLD*. 2021. #LO10.

Phase 2b REEF-1 Trial: Efficacy and Safety of the SiRNA JNJ-3989 And/or the CAM JNJ-6379 for the Treatment of CHB

Patients (%) reaching HBsAg <100 IU/mL at Week 48

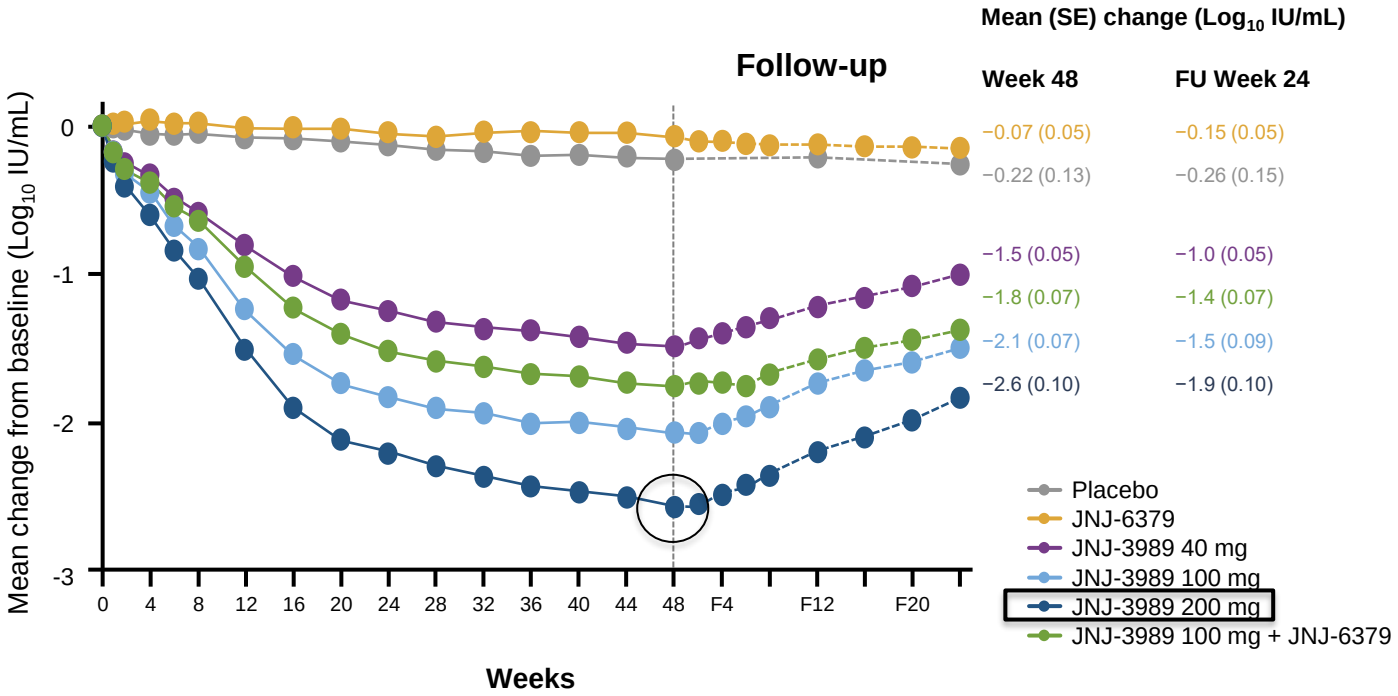


"Antagonistic effect" between siRNA + CAM: mechanism?

Yuen M-F et al. *AASLD*. 2021. #LO10.

Phase 2b REEF-1 Trial: Maximum HBsAg Decline with JNJ-3989 200 mg

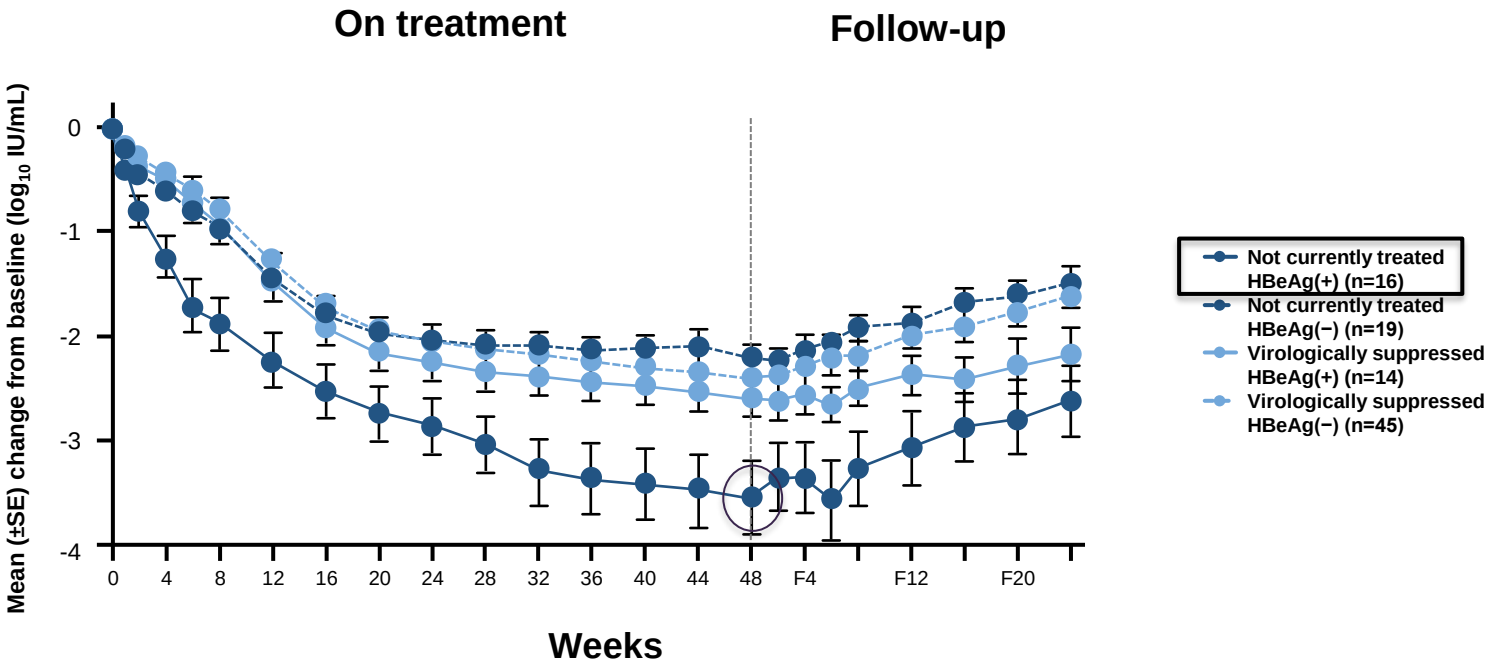
HBsAg



Greatest decline in HBsAg was in the JNJ-3989 200 mg group without CAM

Yuen M-F et al. *AASLD*. 2021. #LO10.

Phase 2B REEF-1 Trial: Greatest Decline in HBeAg+ Not Currently Treated Patients



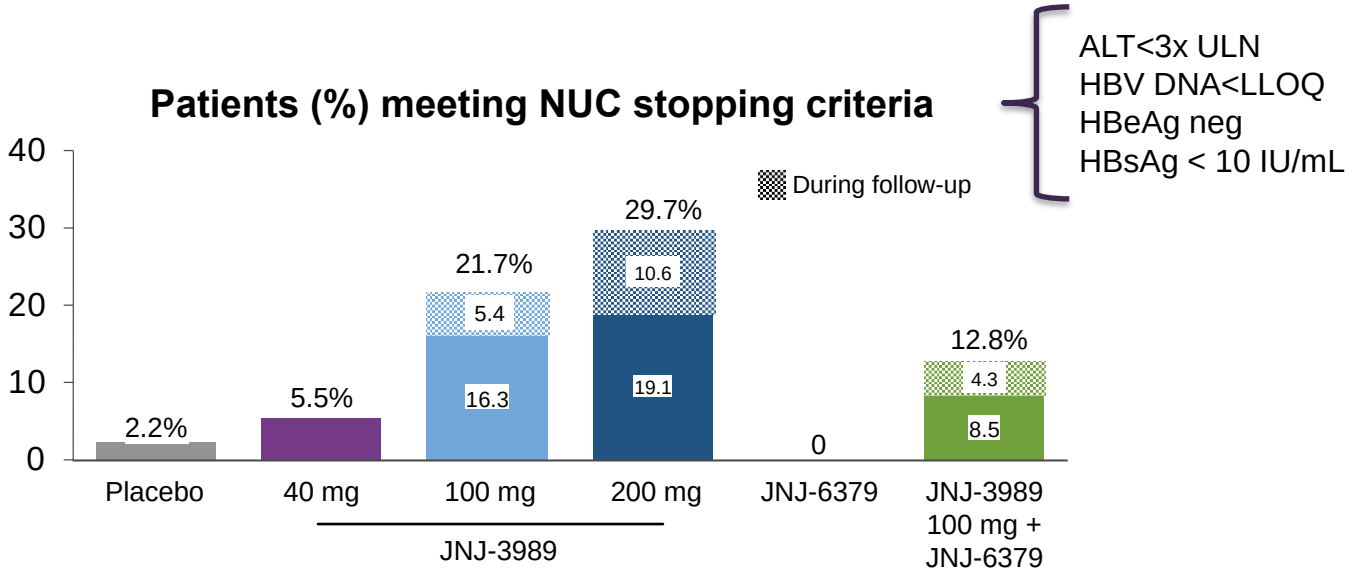
Greatest decline in HBsAg was in the NCT* HBeAg+ patients

*NCT=not currently treated

Yuen M-F et al. *AASLD*. 2021. #LO10.

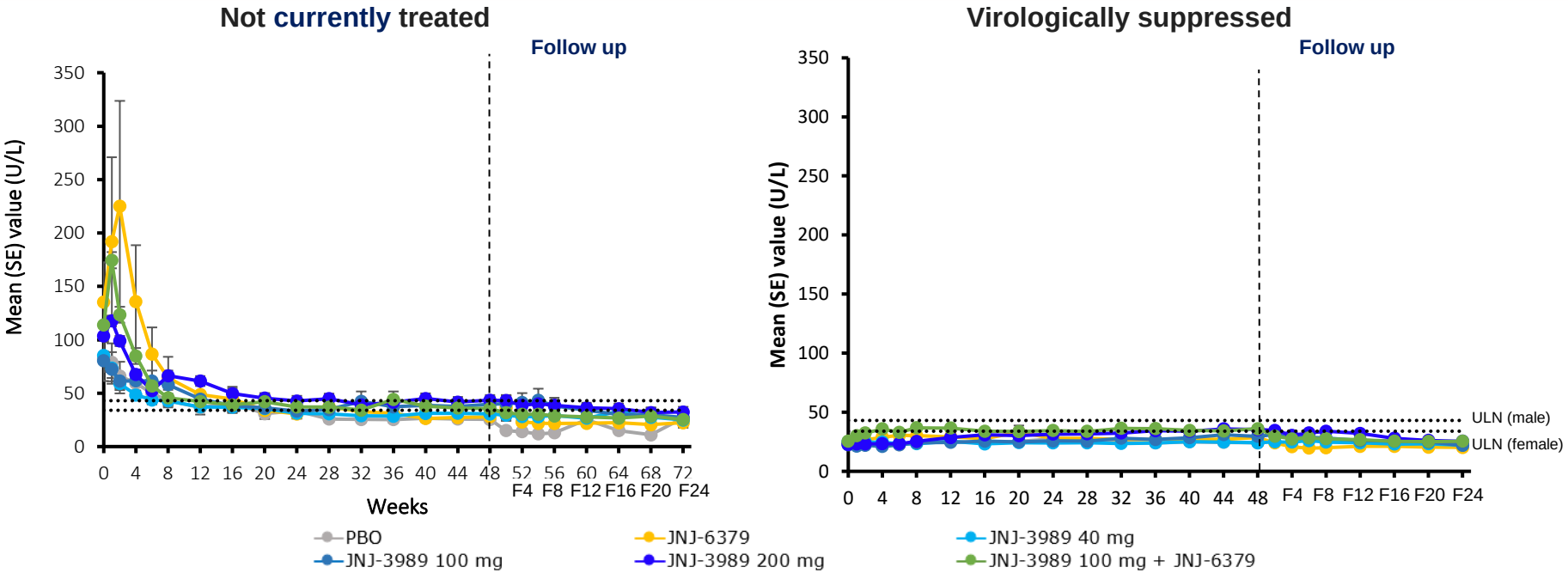
Phase 2b REEF-1 Trial: Efficacy and Safety of the SiRNA JNJ-3989 And/or the CAM JNJ-6379 for the Treatment of CHB

Primary endpoint: Patients (%) meeting NUC stopping criteria at end of treatment



Yuen M-F et al. *AASLD*. 2021. #LO10.

REEF-1: ALT Flares Occurred Infrequently



- **13/470 (2.8%) patients reported ALT flares during treatment; 7/96 patients in the JNJ-3989 200 mg arm had on-treatment ALT flares**
- **1 patient in the JNJ-3989 200 mg arm experienced an ALT flare post-treatment after stopping NA**

*ALT flare: confirmed ALT ≥3× ULN and ≥3× nadir (ie, lowest value observed up to the start of the flare).

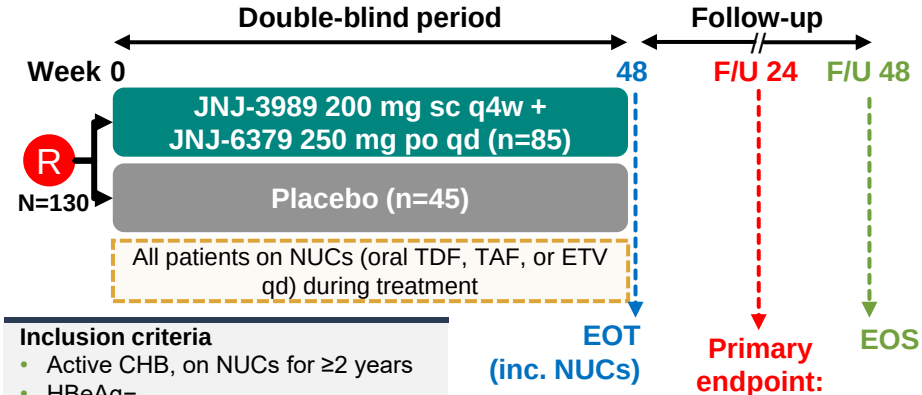
Yuen MF et al. *EASL*. 2022; Slide courtesy of Professor MF Yuen.

REEF-1: Summary

- JNJ-3989 200 mg (highest dose) arm at Week 48
  - 74.7% of achieved HBsAg <100 IU/mL
  - 19.1% patients met primary endpoint (NA stopping criteria)
  - But…no sustained clearance of HBsAg
- All regimens generally well tolerated and safe

Yuen M-F et al. *AASLD*. 2021. #LO10.
Courtesy of Professor MF Yuen.

REEF-2: JNJ-73763989 (SiRNA) and JNJ-56136379 (Bersacapavir, CAM) in HBeAg-Negative Virologically Suppressed CHB Patients



Inclusion criteria
- Active CHB, on NUCs for ≥2 years
- HBeAg−
- ALT <2.0xULN
- HBV DNA <60 IU/mL
- HBsAg >100 IU/mL at screening
- Non-cirrhotic (Fibrosis Stage F0–F2)

HBsAg seroclearance
(HBsAg <LLOQ; 0.05 IU/mL)
at Wk 72 w/o restarting NUCs; EASL 2022

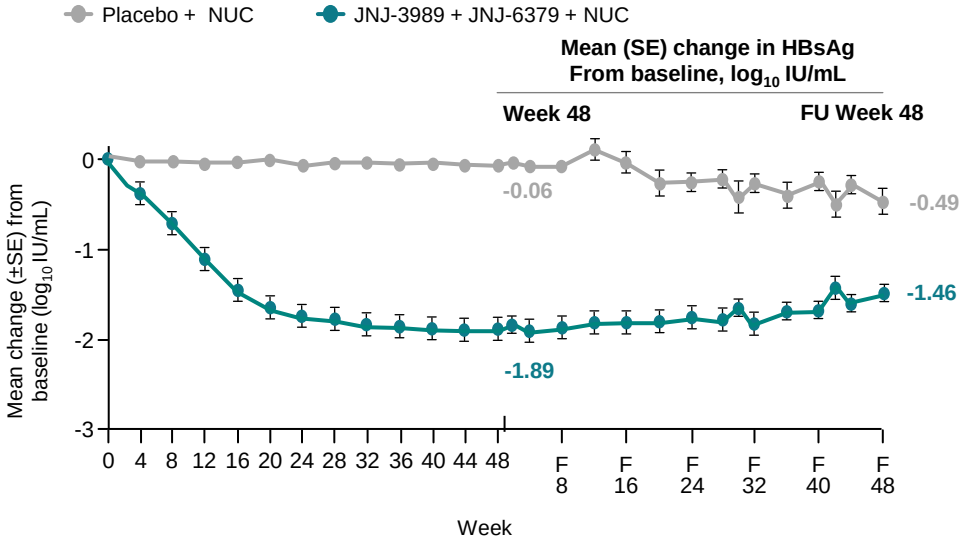
Key point:
All patients stopped study drugs and NUCs at week 48

NUC restart criteria:
- If the below results were confirmed ≥4 weeks apart:
  - HBeAg seroconversion
  - HBV DNA >2000 IU/mL and ALT >5xULN
  - HBV DNA >20,000 IU/mL
- Signs of decreasing/impaired liver function

Additional criteria added during study:
- HBV DNA value >100,000 IU/mL (irrespective of confirmation and/or ALT increase)

Agarwal K et al. *AASLD*. 2022. Late-breaking oral #5012.

REEF-2: JNJ-73763989 (SiRNA) and JNJ-56136379 (Bersacapavir, CAM) in HBeAg-Negative Virologically Suppressed CHB Patients

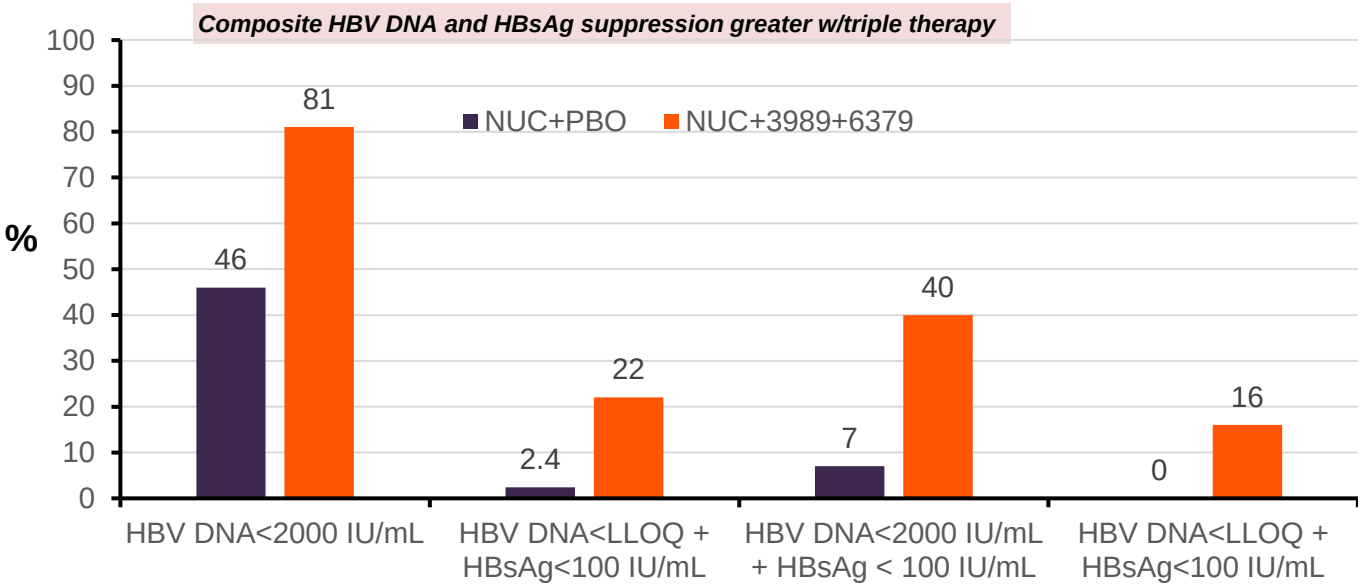


In the JNJ-3989 + JNJ-6379 arm: Sustained viral suppression during f/u 48 weeks

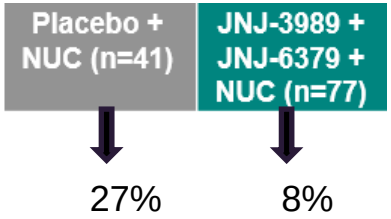
Agarwal K et al. *AASLD*. 2022. Late-breaking oral 5012.

REEF-2: JNJ-73763989 (SiRNA) and JNJ-56136379 (Bersacapavir, CAM) in HBeAg-Negative Virologically Suppressed CHB Patients

Off-treatment HBV DNA and HBsAg suppression at Follow-Up Week 48



Rates of NUC restart



Agarwal K et al. *AASLD*. 2022. Late-breaking oral #5012.

REEF-2: JNJ-73763989 (SiRNA) and JNJ-56136379 (Bersacapavir, CAM) in HBeAg-Negative Virologically Suppressed CHB Patients

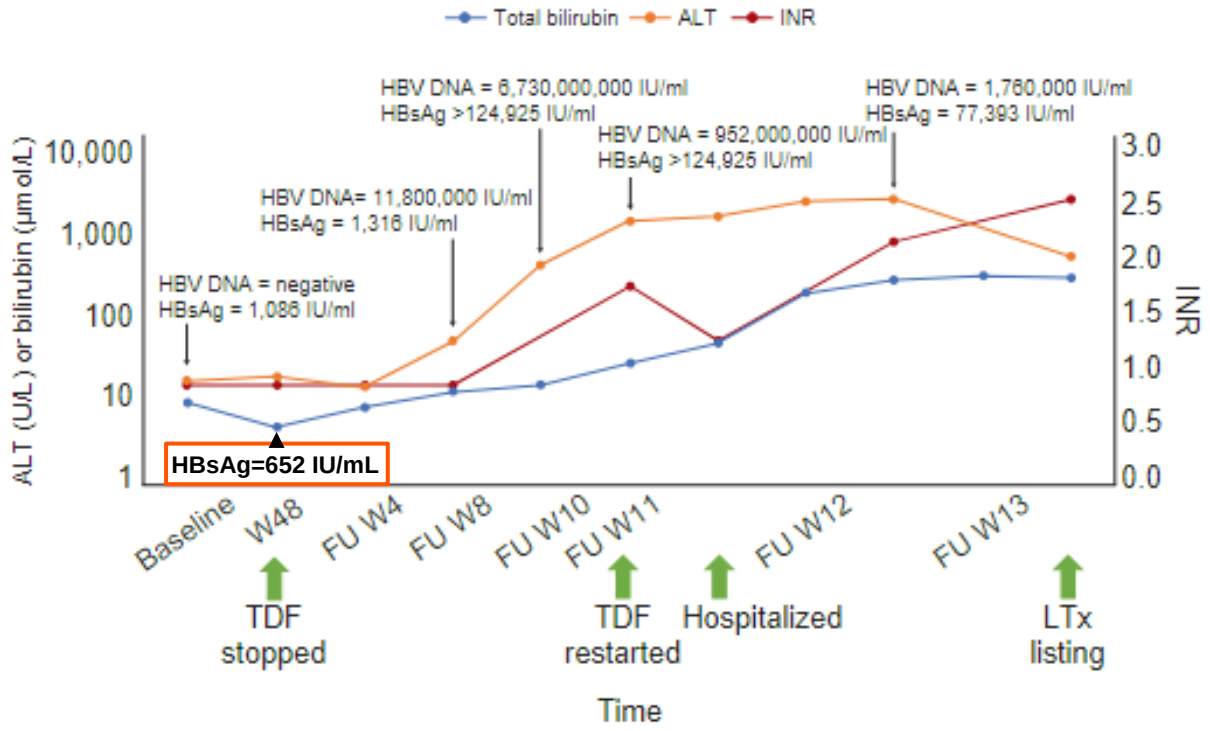
ALT peak level during follow-up

n (%)	Placebo + NUC (n=41)	JNJ-3989 + JNJ-6379 + NUC (n=77)
ALT peak level during follow-up		
<3×ULN	25 (61.0)	73 (94.8)
≥3×ULN to <5 ULN	2 (4.9)	2 (2.6)
≥5×ULN to <10 ULN	4 (9.8)	1 (1.3)
≥10×ULN	10 (24.3)	1 (1.3)

ALT flares much more common during f/u in NUC alone group

Agarwal K et al. *AASLD*. 2022. Late-breaking oral #5012.

Course of the Severe Post-Treatment Flare Patient in REEF-2

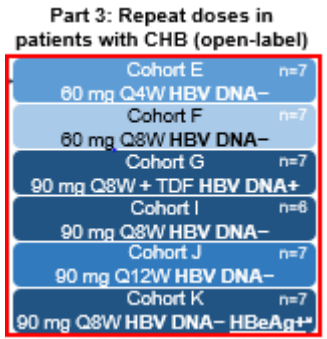


This patient's treatment would not have been stopped In "real life" practice!

Adapted from Agarwal K et al. *J Hepatology*. 2022;77:245-248.

siRNA AB-729 for 48 Wks: Sustained HBsAg Decline at Week 72

- Dose-ranging
- Q4w-Q12W



Change from baseline in HBsAg by visit

Nominal visit	HBV DNA− (on NUC therapy)					HBV DNA+
	Cohort E (n=7)	Cohort F (n=7)	Cohort I (n=6)	Cohort J[a] (n=7)	Cohort K (n=7)	Cohort G (n=7)
Baseline (IU/mL)	3.51 (0.20)	3.53 (0.17)	3.36 (0.23)	3.37 (0.28)	2.23 (0.14)	3.14 (0.14)
Week 12	−1.10 (0.15)	−1.02 (0.11)	−1.30 (0.19)	−1.06 (0.31)	−1.63 (0.39)	−1.56 (0.32)
Week 24	−1.84 (0.16)	−1.57 (0.09)	−1.80 (0.23)	−1.56 (0.25)	−1.99 (0.35)	−1.82 (0.29)
Week 36	−1.84 (0.19)	−1.78 (0.10)	−2.06 (0.28)	−1.79 (0.39)	−2.50 (0.39)	−2.08 (0.32)
Week 48	−1.89 (0.18)	−1.90 (0.14)	−1.91 (0.32)	−1.80[b] (0.41)		−2.15 (0.34)
Week 12 post last dose	−1.81 (0.17)	−1.74 (0.16)	−1.77 (0.31)	−1.80[b] (0.41)		−1.97 (0.28)
Week 24 post last dose	−1.54 (0.19)	−1.48 (0.24)	−1.67 (0.40)	−1.52 (0.40)		−1.59 (0.31)

[a]One patient chose not to extend treatment after Week 24; [b]Week 48 and 12 weeks post last dose are at the same visit for Cohort J

- Mean declines in HBsAg were comparable across all cohorts

T cell activation and decline in exhausted T cells
- Thi EP et al, EASL 2022 SAT397

- F/U at AASLD 2022
- 2 HBeAg+ patients w/ sustained clearance of HBsAg

-Yuen M-F at, AASLD 2022 LB5047

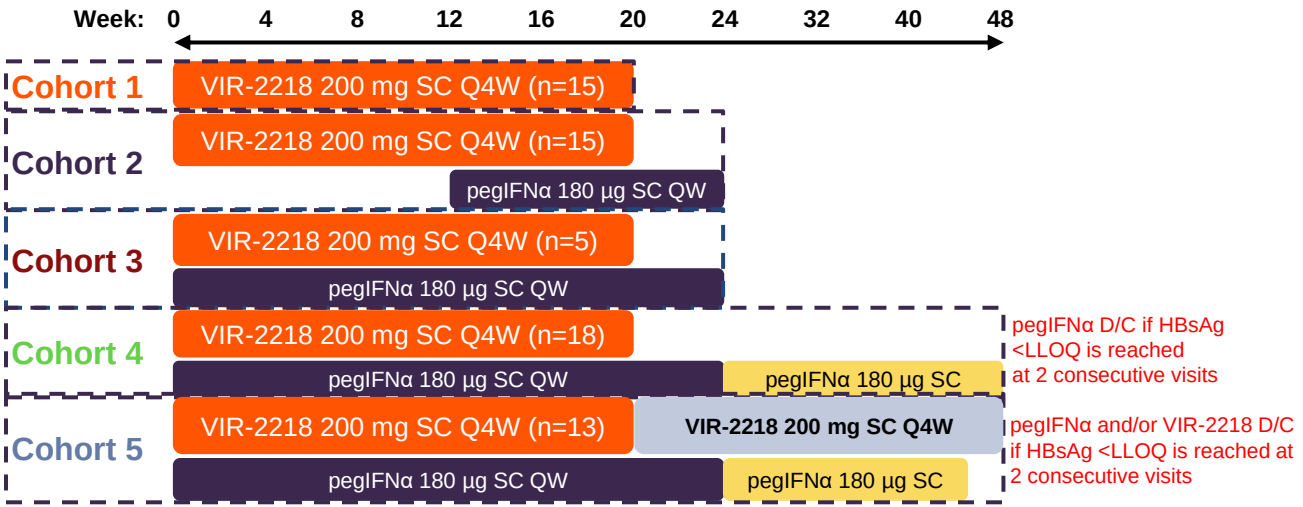
Yuen MF, et al. EASL 2022. #SAT443

Preliminary 48-Week Safety and Efficacy of VIR-2218 (SiRNA) Alone or in Combination With PegIFNα in CHB

Five dosing regimens in patients with CHB up to 28 weeks post-last dose

Key inclusion criteria

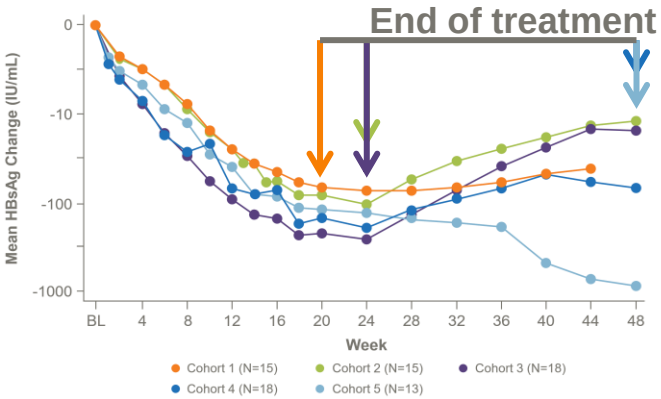
- Age 18–65 years
- Detectable HBsAg for ≥6 months
- On NUC therapy for ≥2 months
- HBsAg >50 IU/mL
- HBV DNA <90 IU/mL
- F3 on bx or LSM >8.5 kPa



Yuen M-F et al. *AASLD*. 2022. Oral #19.

Preliminary 48-Week Safety and Efficacy of VIR-2218 (SiRNA) Alone or in Combination With PegIFNα in CHB

Reduction in HBsAg from baseline



	HBsAg log Mean change from baseline			
	Week 24	Week 36	Week 44	Week 48
Cohort 1	-1.9	-1.8	-1.6	NA
Cohort 2	-2.0	-1.4	-1.1	-1.1
Cohort 3	-2.4	-1.6	-1.2	-1.2
Cohort 4	-2.3	-1.8	-1.8	-1.8
Cohort 5	-2.1	-2.3	-2.9	-2.9

Proportion with HBsAg loss during study

Participants with HBsAg seroclearance, n (%)	Cohort 1 (n=15)	Cohort 2 (n=15)	Cohort 3 (n=18)	Cohort 4 (n=18)	Cohort 5 (n=13)
	VIR-2218 x6	VIR-2218 x 6 lead-in + PEG-IFNα x 12	VIR-2218 x 6 + PEG-IFNα x 24	VIR-2218 x 6 + PEG-IFNα x ≤48	VIR-2218 x 13 + PEG-IFNα x ≤ 44
At any time up to Week 48	0 (0%)	1 (6.7%)	1 (5.6%)	4 (22.2%)	4 (30.8%)
At Week 48	0 (0%)	1 (6.7%)	0 (0%)	3 (16.7%)	4 (30.8%)
With Anti-HBs (>10 mIU/mL) at Week 48	0 (0%)	1 (6.7%)	0 (0%)	3 (16.7%)	4 (30.8%)

Yuen M-F et al. *AASLD*. 2022. Oral #19.

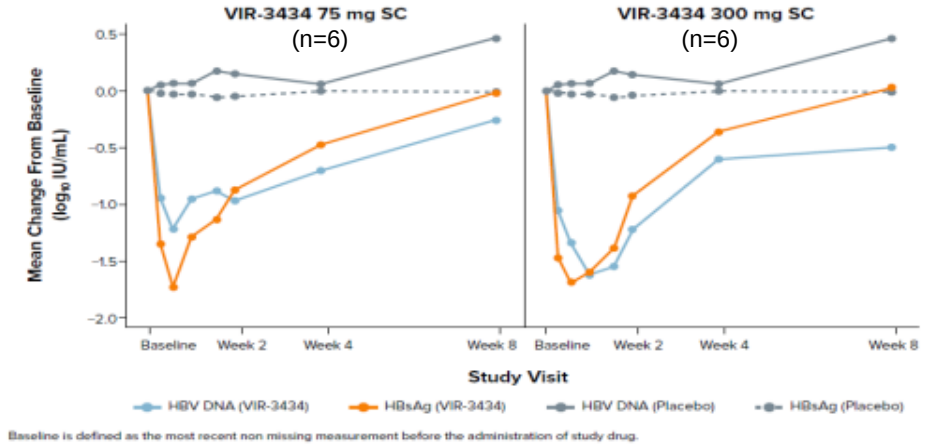
What Clinicians Usually Say About Duration of IFN as a Potential Component of Novel HBV Regimens

12 weeks	24 weeks	48 weeks
“Acceptable”	“Hmm…Maybe”	“Please no, not again!”

Interferon is an active agent in the investigative arena

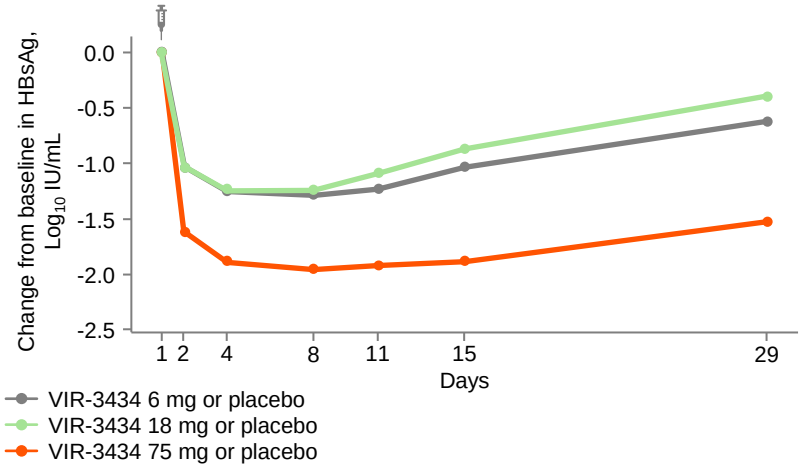
Reduction in HBV DNA and HBsAg Following a Single Dose of VIR-3434 (Monoclonal Anti-HBs): Patients With Viremia

Mean change from baseline in HBsAg and HBV DNA



Baseline is defined as the most recent non missing measurement before the administration of study drug.

AASLD 2021, #P839: Mean change from baseline in HBsAg in virally suppressed patients



Recent data suggest additive effect of mAb + siRNA (VIR-2218) on HBsAg reduction
Gane E et al. *AASLD*. 2022. Oral #18.

Agarwal K et al. *AASLD*. 2022. Poster #1187.

Monoclonal Antibodies: Two Potential Mechanisms of Action

Reduction of HBsAg may reduce T cell exhaustion and promote immune-mediated viral clearance

Neutralizing antibodies may inhibit viral entry

- Role of monoclonal antibodies may be adjunctive to other therapies
- Expect combination studies

A Landmark Publication in the Quest for Functional Cure of HBV

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Bepirovirsen in Chronic Hepatitis B Infection

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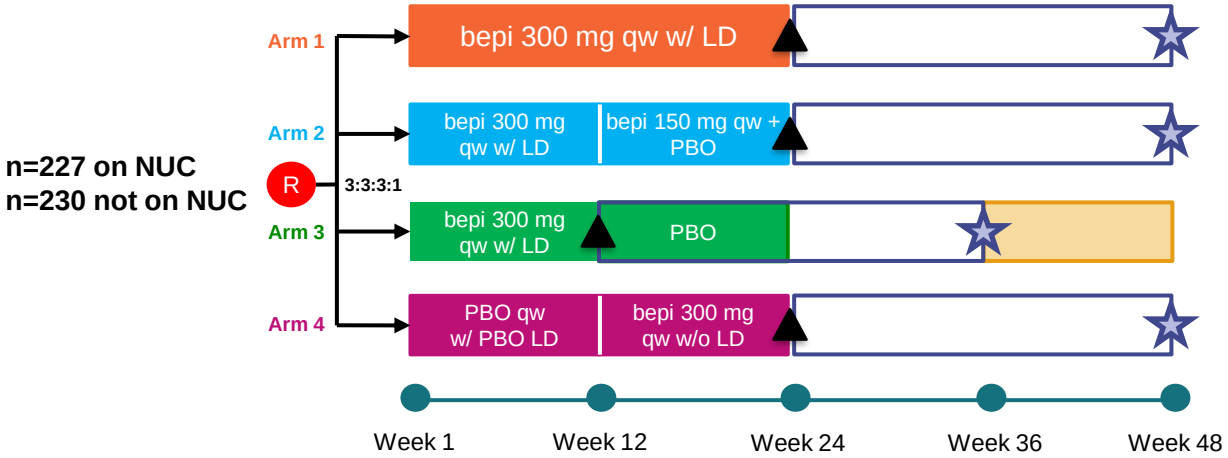
Yuen MF et al. *N Engl J Med*. Nov 8, 2022;387:1957-68.

B-Clear: Study Design



Stratification

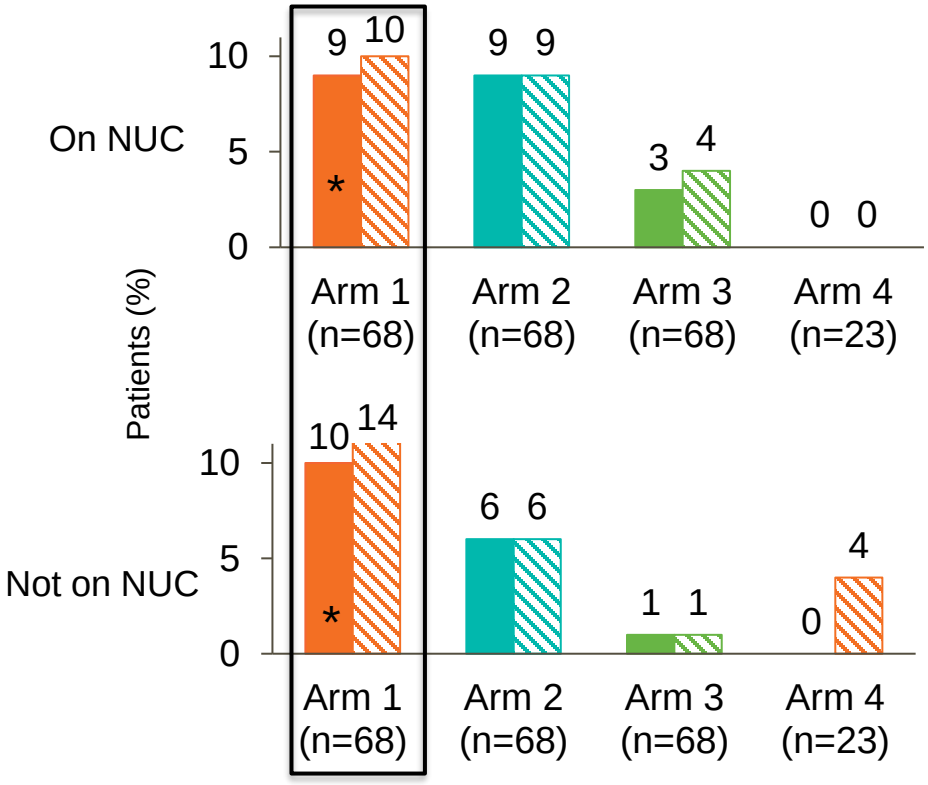
- HBsAg ≤3 $\log_{10}$ IU/mL or >3 $\log_{10}$ IU/mL

Primary endpoint: HBsAg <LLOD (0.05 IU/mL) and HBV DNA <LLOQ (20 IU/mL) sustained for 24 weeks from planned end of bepirovirsen treatment in the absence of newly initiated antiviral treatment.

Note: Participants on stable NA therapy were expected to continue NA therapy during the study.

Yuen M-F et al. *AASLD*. 2022. Late-breaking oral #5015.

B-Clear: Patients Achieving Primary Outcome or Modified Primary Outcome



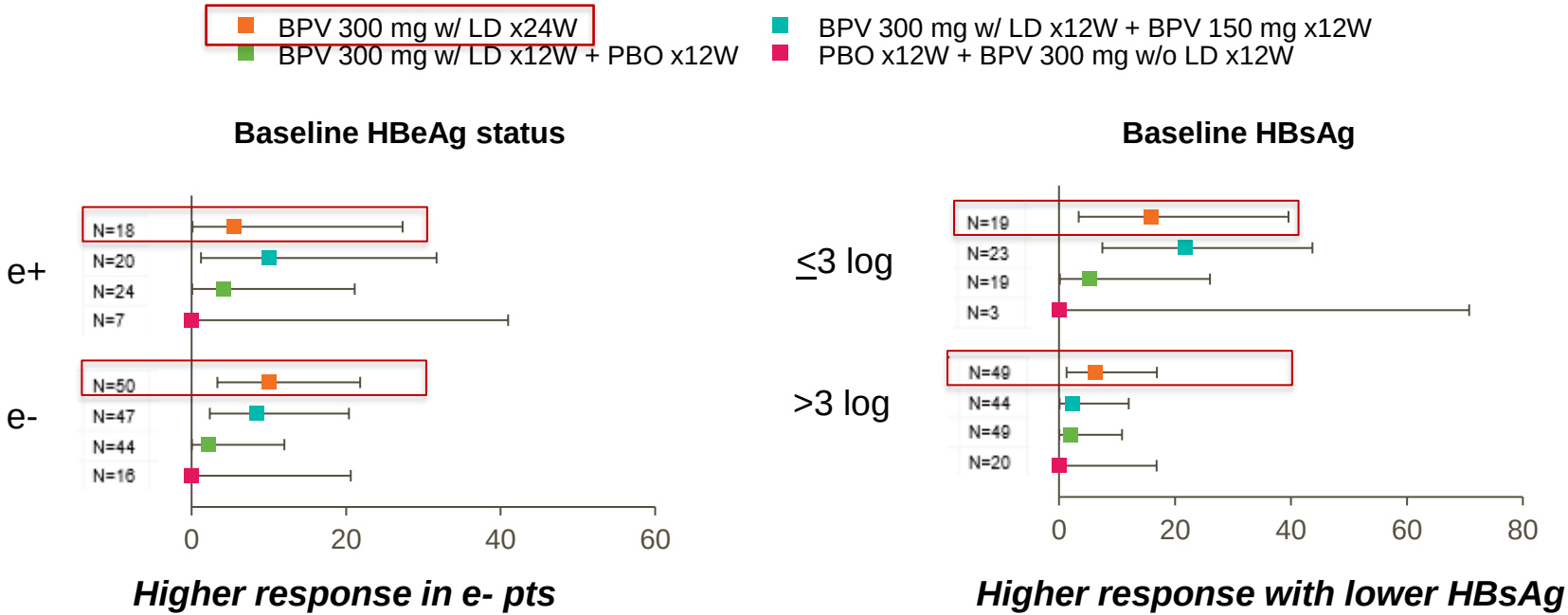
BPV 300 mg w/ LD x24W
BPV 300 mg w/ LD x12W + BPV 150 mg x12W
BPV 300 mg w/ LD x12W + PBO x12W
PBO x12W + BPV 300 mg w/o LD x12W

Primary outcome
Modified primary outcome, which permitted "blips" – single time point increase in HBsAg ≥LLOD or HBV DNA ≥LLOQ – in response

*HBsAg < 0.05 IU/mL in 26-29% at EOT

Yuen M-F et al. *AASLD*. 2022. Late-breaking oral #5015.
Lim S-G. *AASLD*. 2022. Late-breaking poster #5022.

B-Clear: Baseline HBeAg and HBsAg and Sustained Response: Patients on NUC



Higher response in e- pts

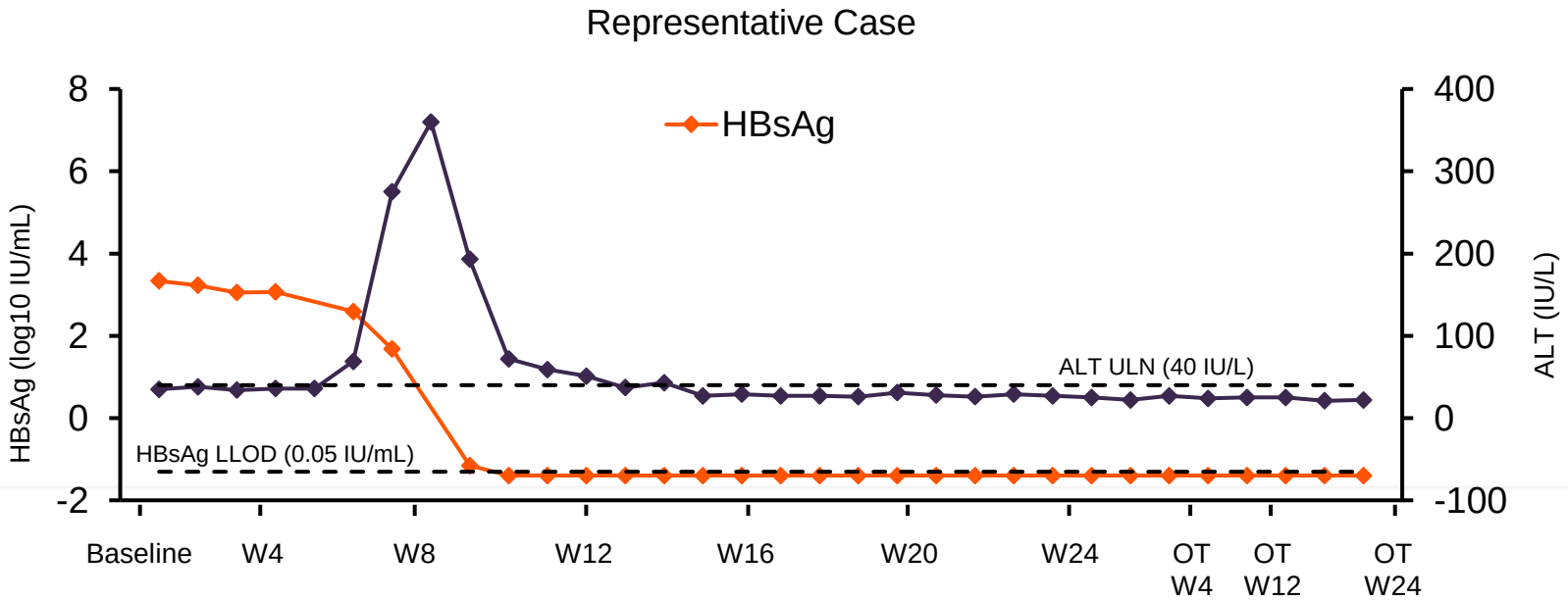
Higher response with lower HBsAg

Similar patterns in patients not on NUC

Yuen M-F et al. *AASLD*. 21022. LB Oral #5015.

B-Clear: Most ALT Elevations Occurred in Association With HBsAg Decline

- **39 participants had ALT increase ≥3 x ULN; most (97%) elevations occurred in association with HBsAg decline (>0.4 log from baseline).**



Yuen M-F et al. *AASLD*. 2002; LB oral 5012; Slide courtesy of Professor M-F Yuen.

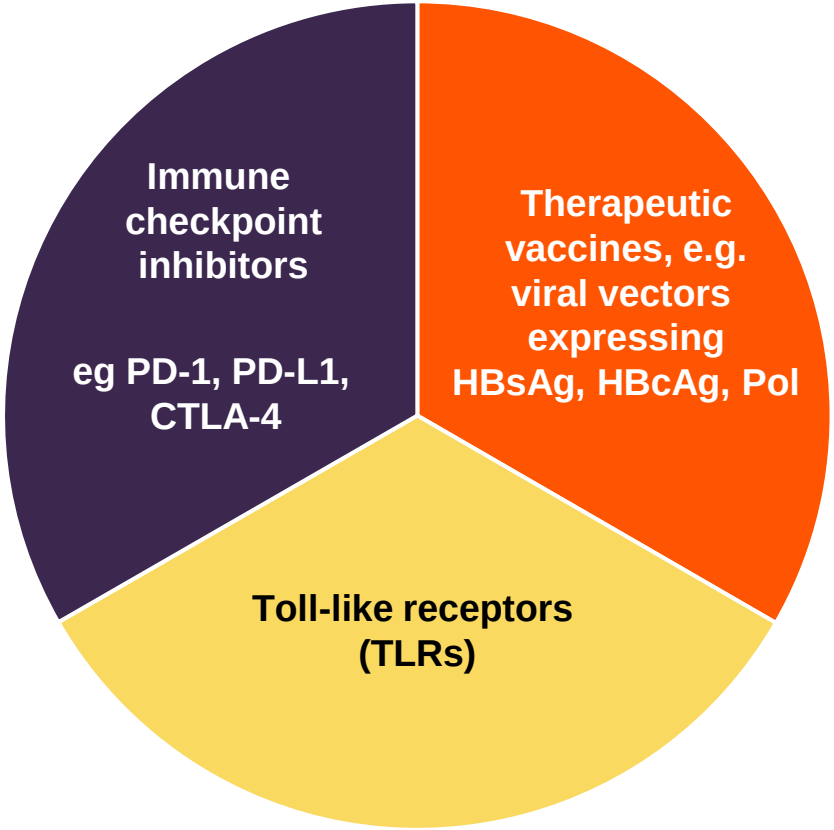
ALT Flares: “Good” or “Bad”?

“The occurrence of ALT flares is a reliable marker of immune restoration and possible subsequent control…Therefore, the occurrence of ALT flares should not be a concern with new HBV drugs and should be expected as a necessary marker of subsequent efficacy…Two important issues, however…

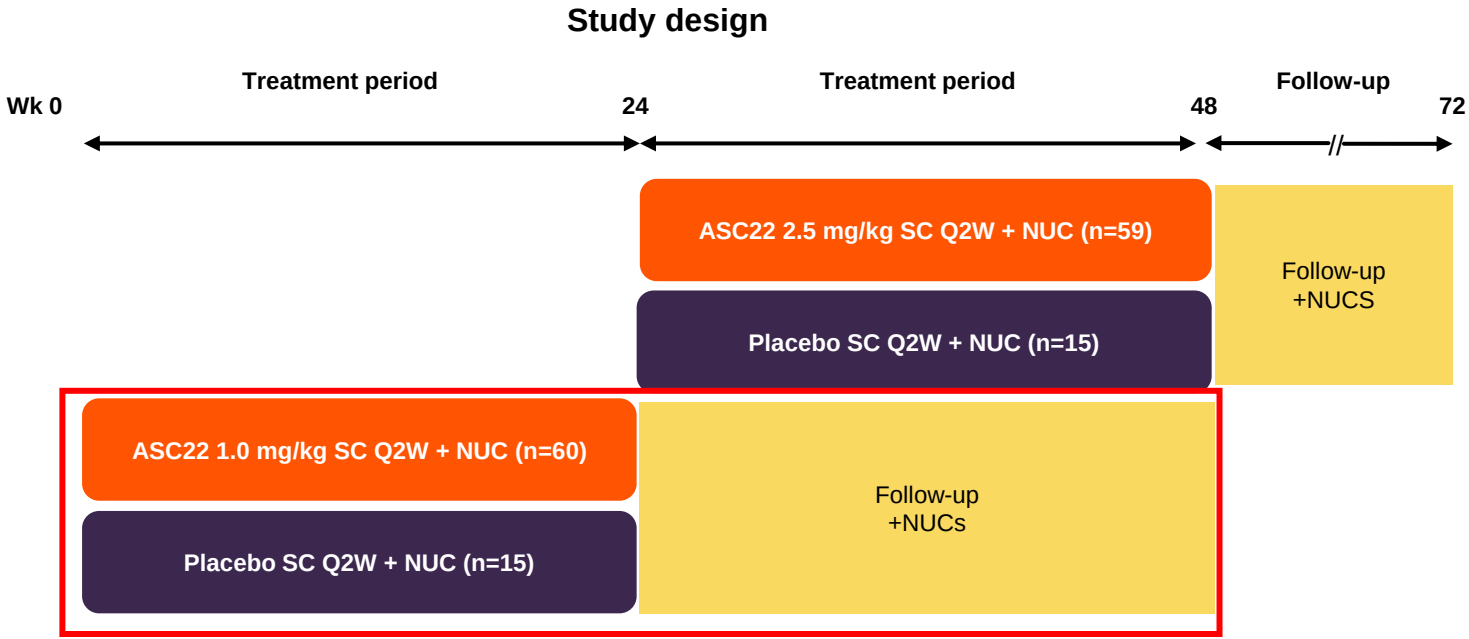
First, immune restoration is difficult to differentiate from drug-induced liver toxicity, especially at the earliest stages of clinical development. Second, the strength of immune control is impossible to control when it occurs. If it is too strong, ALT flares are dangerous as they expose patients to acute hepatic failure and liver transplantation. If it is too weak, ALT flares are not associated with a sustained control of the disease.”

Pawlotsky JM. *Lancet Gastroenterology and Hepatology*, available online 4 November 2022.

Immunotherapies With Potential Utility in Chronic Hepatitis B



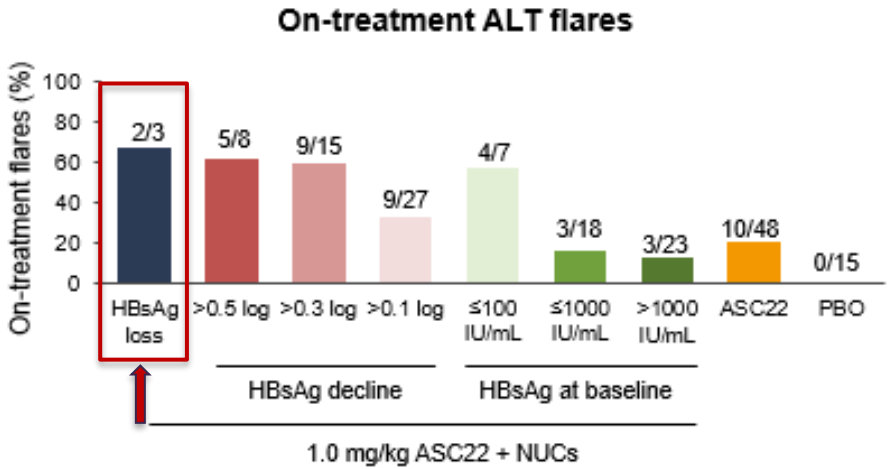
Phase 2B Study of PD-L1 Ab ASC22 (Envafolimab) Plus NUCs (Interim Results)



Safety population: 60+15
FAS: 48+15
10 dropouts

Wang G et al. *EASL*. 2022. OS091.

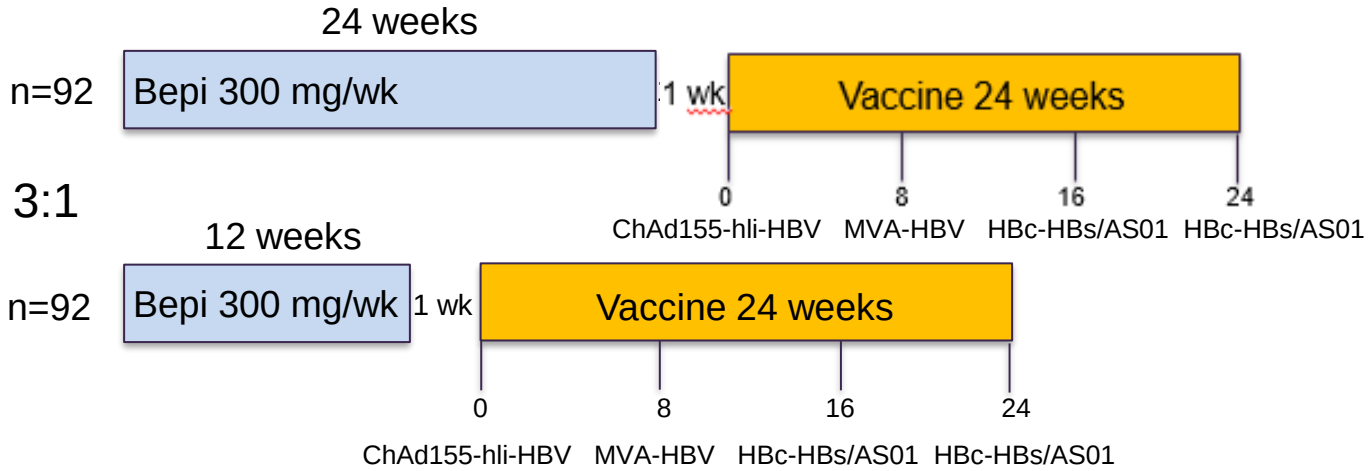
Phase 2B Study of PD-L1 Ab ASC22 (Envafolimab) Plus NUCs (Interim Results)



- 9/10 patients with ALT flares showed an obvious downward trend of serum HBsAg
- 2/3 patients with sustained HBsAg loss experienced ALT flares

Wang G et al. *EASL*. 2022. #OS091. Sponsored by Ascletis.

Ongoing Trial of Bepiroversen Followed by Therapeutic HBV Vaccines



ChAd: Chimpanzee adenovirus HBV vaccine
MVA: Modified Vaccina Ankara

Adapted from:
https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/2021-003567-10_annex_iiia_mva-hbv.pdf

Where Do We Stand in Early 2023?

- SiRNA therapy + NUCs cannot effect functional cure (FC) on their own (more than perhaps rarely)
- ASOs capable of FC but not frequently enough to become a standalone therapy – perhaps in patients with low HBsAg levels at baseline
- Post-treatment suppression: mechanisms?
- Importance of ALT flares must be studied further: correlation with clearance?
- Interest in CAM's being revived with development of more potent agents that appear to affect "secondary mechanisms"
- Combination therapies (eg antiviral + immunomodulatory) being studied