Results of clinical trials of novel cure strategies

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Disclosures: , Merck, Janssen, Gilead, Boehringer Ingelheim, BMS, Novartis, Roche, AbbVie, GSK, Vertex, Idenix, Intercept, Precision BioSciences

HBV cure Task Force

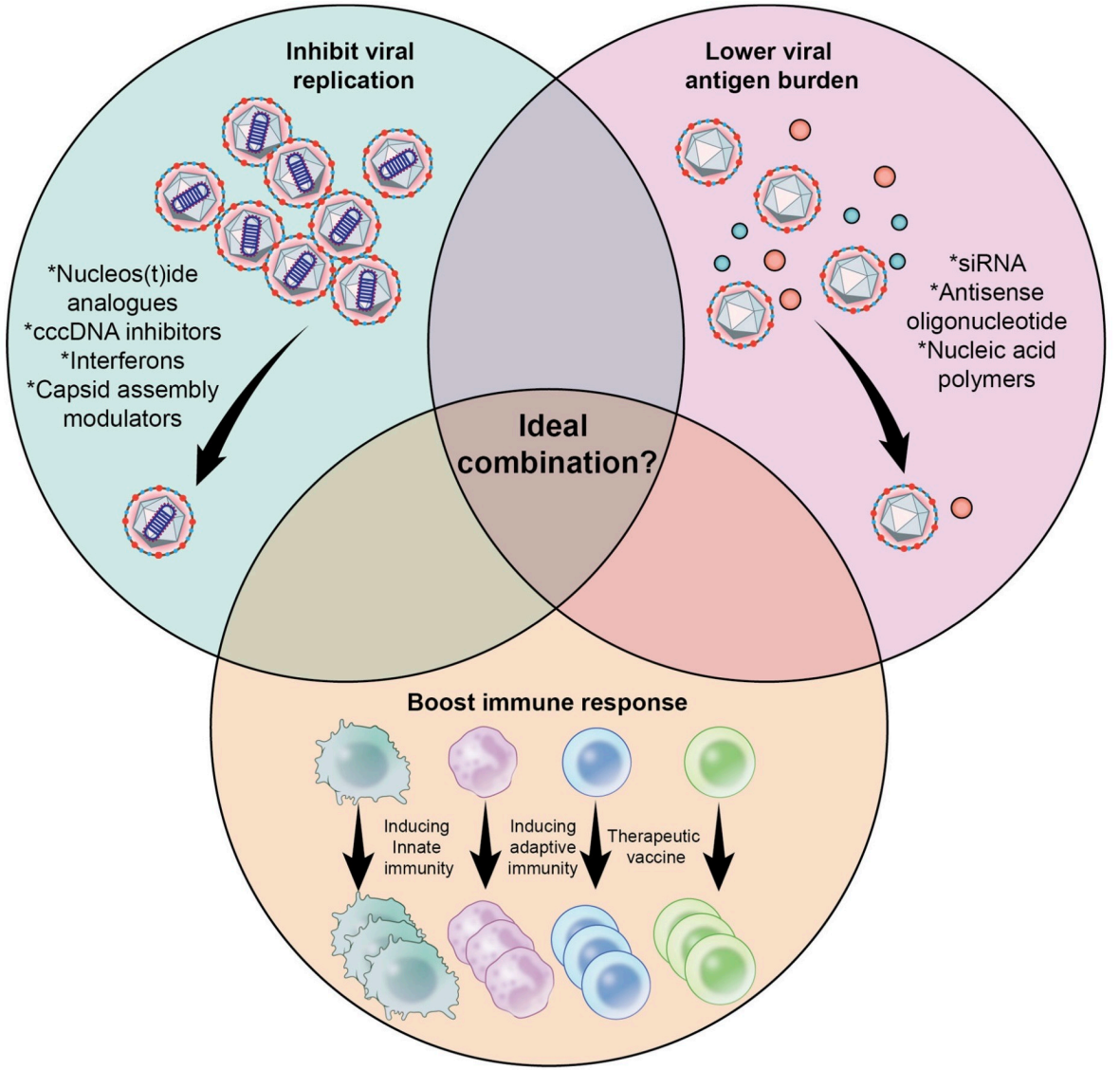
RB-RNA

Endorsed by

ICE-HBV
International Coalition to Eliminate HBV

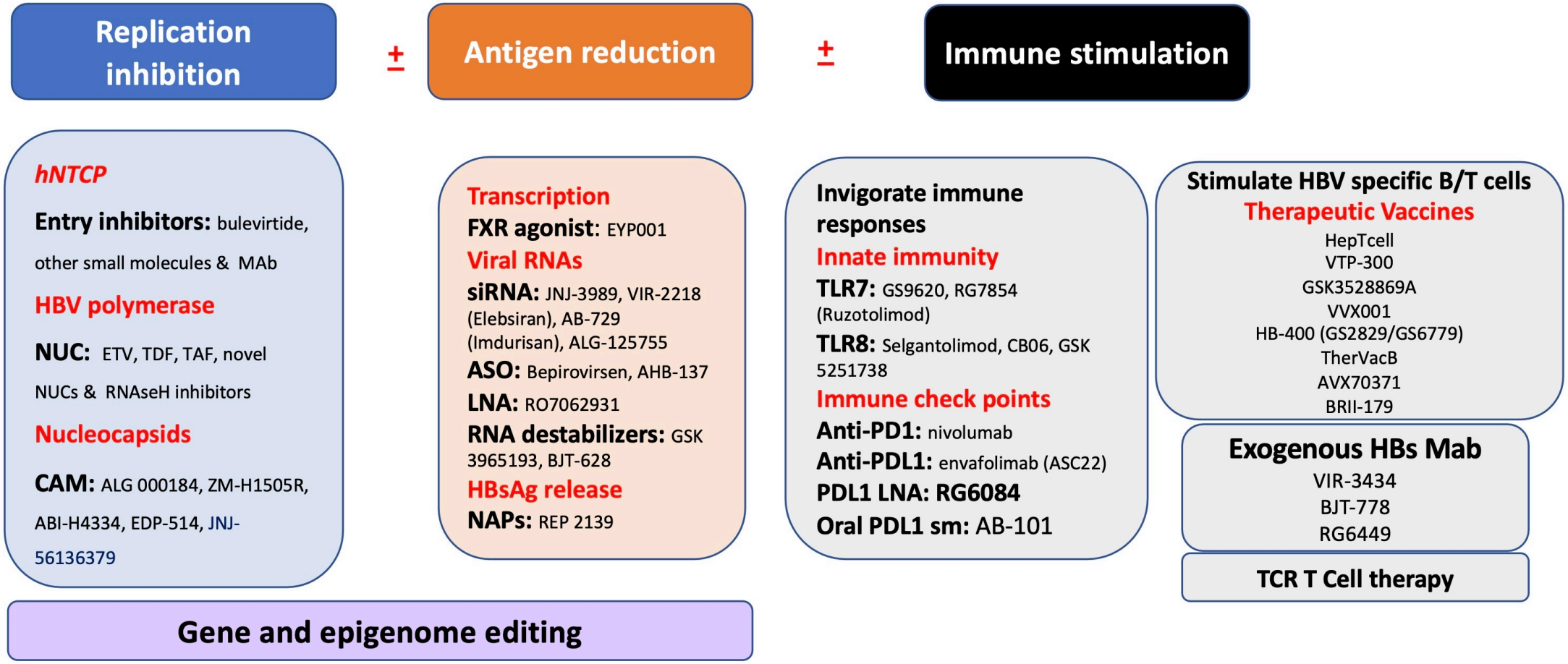
IP-cure-B

potential combination for HBV functional cure



Gopalakrishna H , Ghany MG. Curr Hepatol Rep 2024; 23: 241-252

HBV drug pipeline and the potential for combination therapy to cure HBV

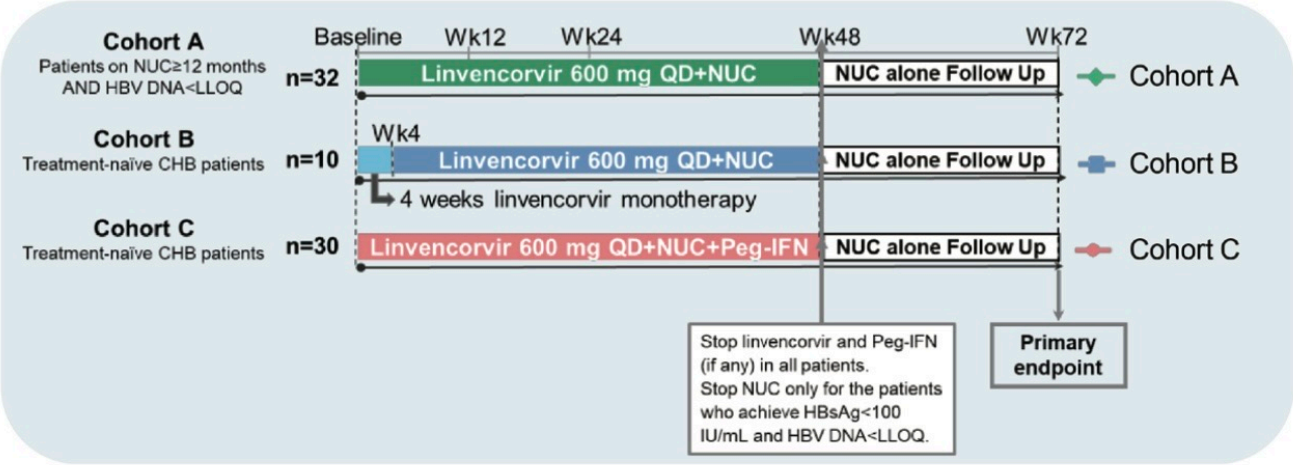


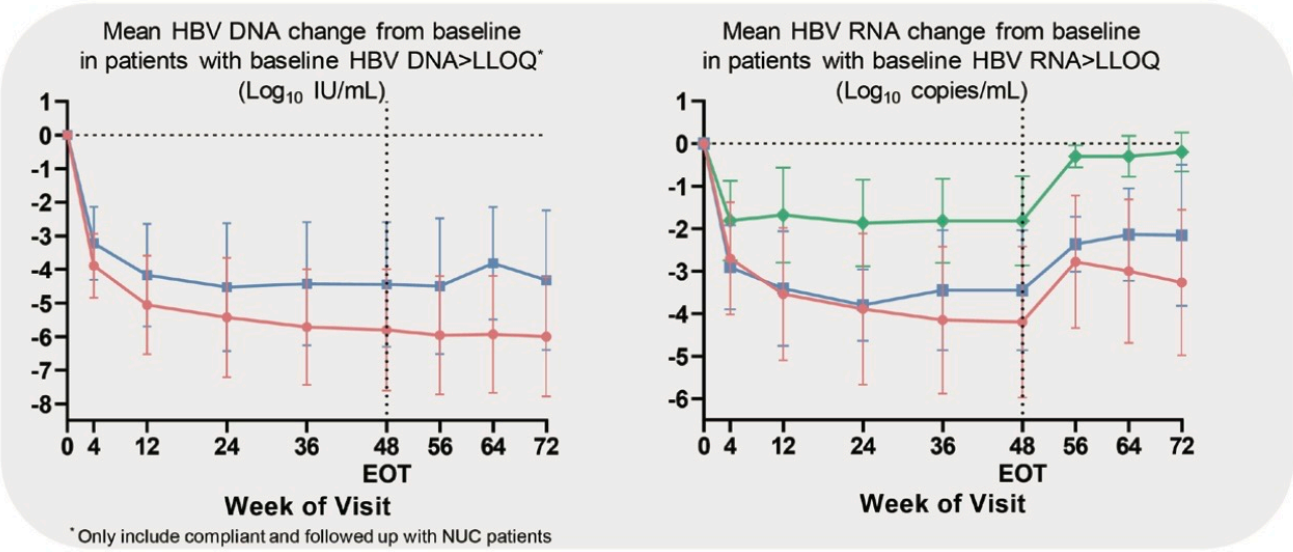
Fanning et al. Nat Rev Drug Discov. 2019; Revill et al, Lancet Gastroenterol Hepatol 2019; Lim et al Nat Rev Gastroenterol Hepatol. 2023; Feld et al, Clin Gastroenterol Hepatol 2023; https://www.hepb.org/treatment-and-management/drug-watch

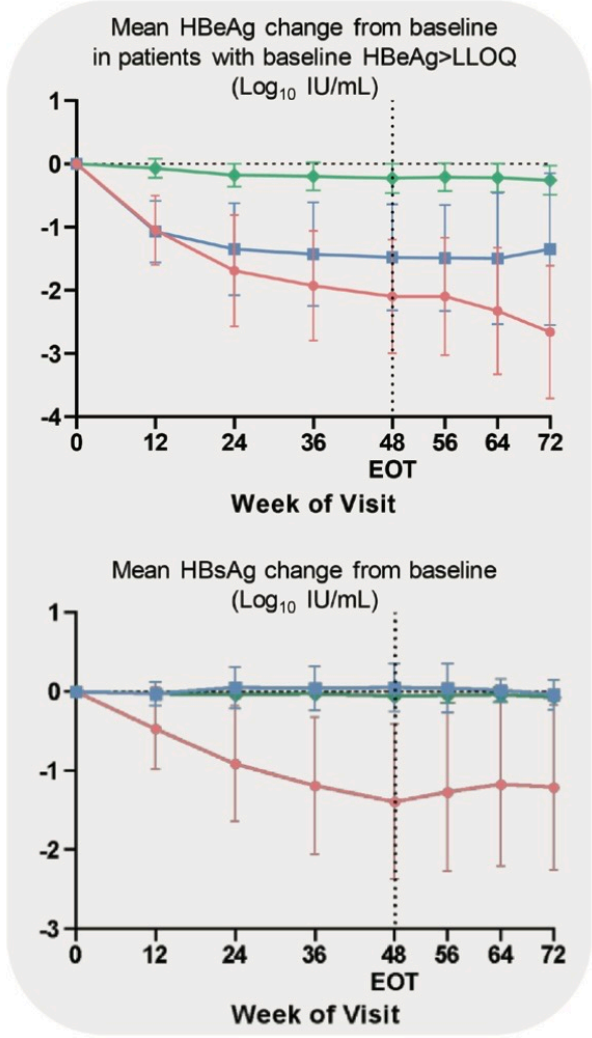
Courtesy Fabien, Zoulim

CAM-A Linvencorvir (RO7049389) for 48 weeks in combination with NUC ± PegIFN decreases HBVDNA and antigens but without FC

Open label Phase 2 study



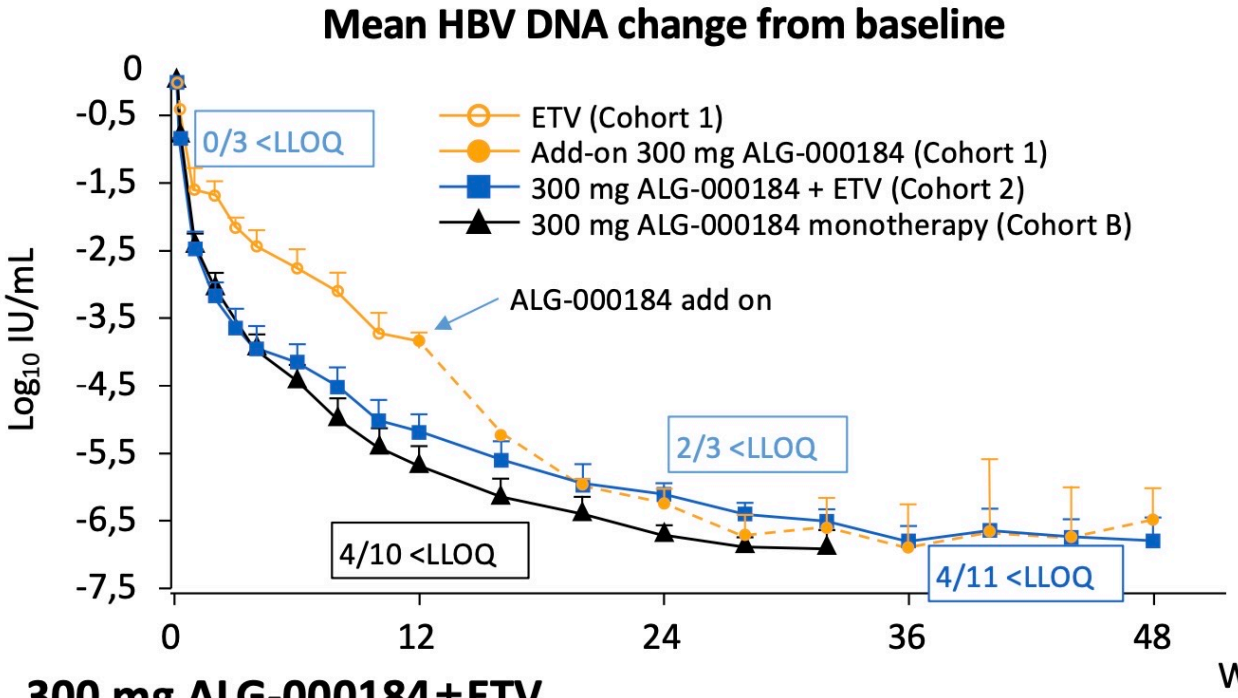


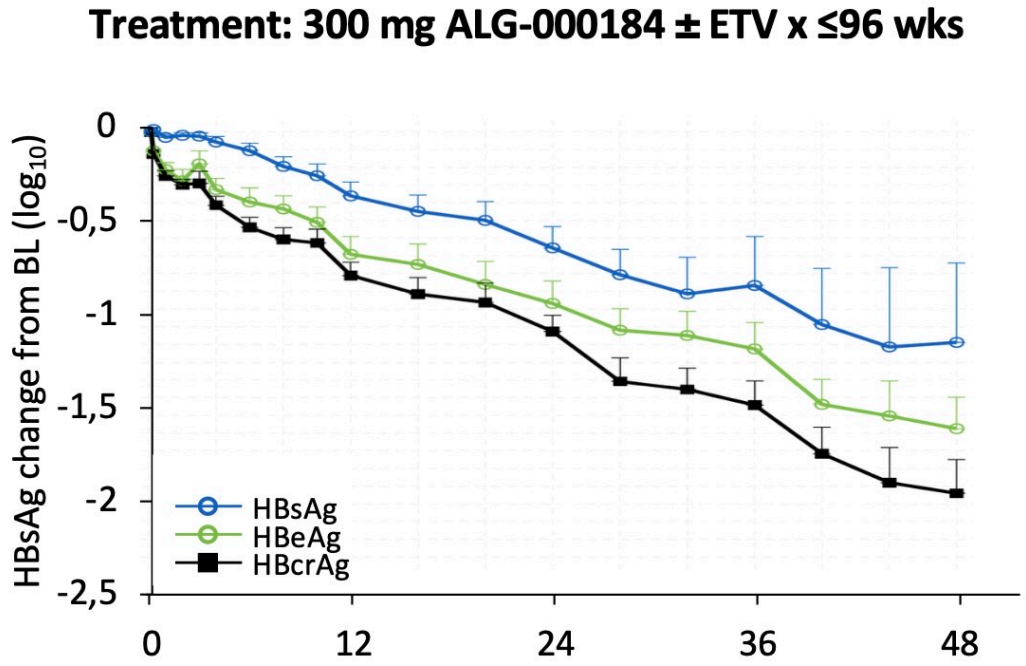


- Linvencovir plus SoC was safe and well tolerated
- Demonstrated potent suppression of HBVDNA and RNA in Trt naïve pts
- Reduced HBeAg and HBCrAg in Trt naïve pts
- No decline in HBsAg
- Triple Trt with Peg-IFN led to obvious decline in Trt naïve pts including GT-C
- No HBsAg loss was achieved

Hou J & Yuen MF et al. Clin Mol Hepatology 2024 : 30 : 191-205

Second generation CAM ALG-000184 for 48 weeks decreases HBV DNA and antigens in untreated HBeAg-positive CHB patients





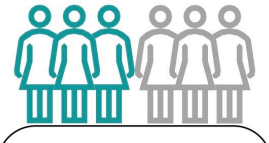
- Showed greater HBV DNA reduction than ETV monotherapy (mean maximum reduction 6.8 logs, 40% <LLOQ)
- No viral breakthrough was observed in ALG-000184 monotherapy x ≤44 weeks
- Mean maximum reduction of HBV RNA 4.5 log c/mL, 64% <LLOQ
- Decline in viral antigen levels

Yuen MF et al. AASLD2023: LB 5028

Results of siRNA in combination therapy

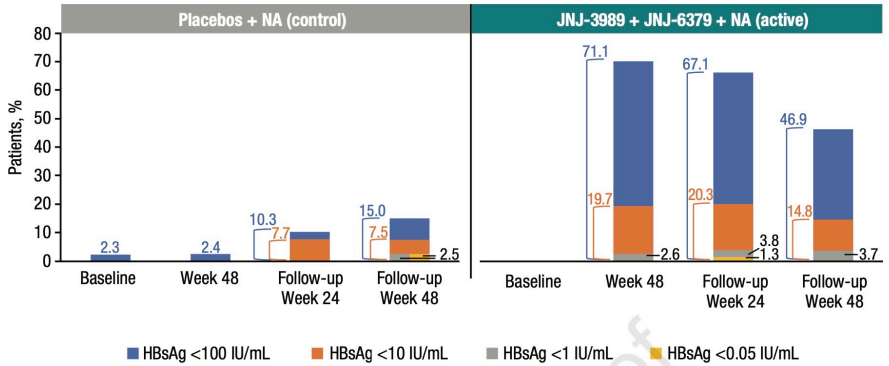
- With other DAAs
- With TLR agonists
- With monoclonal antibodies
- With low dose PD-1 inhibitor
- With Therapeutic Vaccines

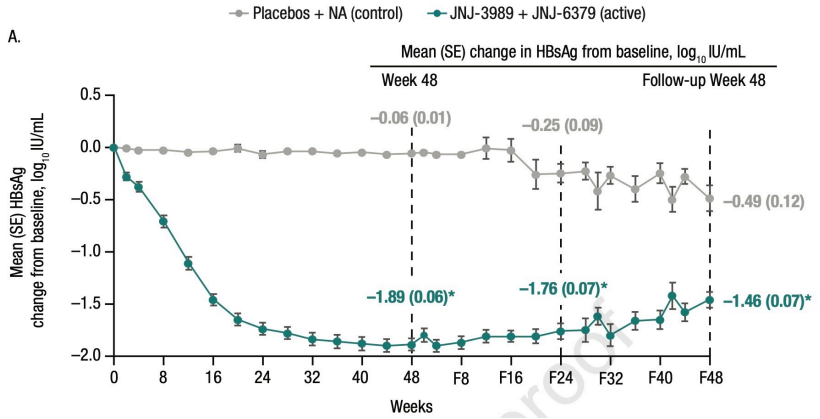
REEF-2: Reduction in HBsAg without FC among virologically-suppressed HBeAg-negative CHB treated for 48 weeks with JNJ-3989 (siRNA) and JNJ-JNJ-6379 bersacapavir (CAM)



CHB diagnosis
NA suppressed
HBeAg–

Active treatment group: JNJ-3989 (200 mg SC Q4W) + JNJ-6379 (250 mg PO QD) + NA N = 85	**Results**	**Control group:** JNJ-3989 placebo + JNJ-6379 placebo + NA N = 45
• Mean HBsAg decline = –1.89 log_{10} IU/mL • 15.6% had HBV DNA <LLOQ and HBsAg <100 IU/mL (partial cure)	**Week 48 (end of all treatment)**	• Mean HBsAg decline = –0.06 log_{10} IU/mL • 0 had HBV DNA <LLOQ and HBsAg <100 IU/mL (partial cure)
No functional cure (primary endpoint)	**Follow-up Week 24**	No functional cure (primary endpoint)
• No functional cure • 81.5% had HBsAg reductions from baseline >1 log_{10} IU/mL • 46.9% had HBsAg <100 IU/mL • Lower frequency of HBV DNA relapse and ALT increases • 9.1% restarted NA	**Follow-up Week 48 (end of study)**	• No functional cure • 12.5% had HBsAg reductions from baseline >1 log_{10} IU/mL • 15.0% had HBsAg <100 IU/mL • Higher frequency of HBV DNA relapse and ALT increases • 26.8% restarted NA





Agarwal K et al. J Hepatol 2024

Off-treatment responses following 48 weeks of Imdusiram (AB-729,siRNA), NUC and vebicorvir (VBR, CAM) combination in virologically suppressed patients with HBeAg-negative CHB

- No participants met the protocol-mandated NUC restart criteria or had ALT ≥2× ULN during follow-up
- Participants who maintained HBV DNA <LLOQ and/or HBsAg <100 IU/mL are shown below

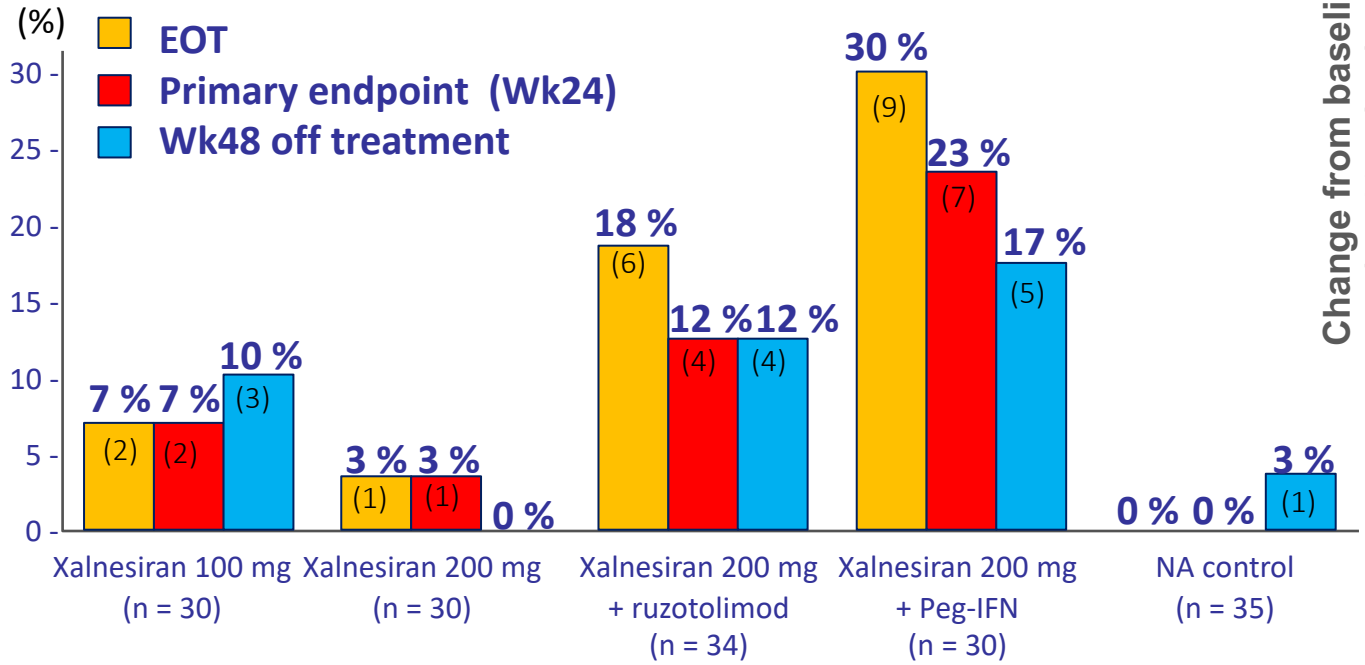
n/N (%)		Off-treatment week									
		4	8	12	16	20	24	28	32	36	40
HBV DNA <LLOQ	Imdusiran + NUC	7/7	5/6	5/6	3/5	0/3	0/3	0/2	0/1	0/1	0/1
	VBR + imdusiran + NUC	8/12	6/10	3/6	1/5	1/3	1/3	1/2	2/2	1/2	NA
HBsAg <100 IU/mL	Imdusiran + NUC	6/7	5/6	5/6	4/5	1/2	2/3	1/2	1/1	0/1	0/1
	VBR + imdusiran + NUC	12/12	8/9	5/6	4/4	3/3	3/3	2/2	2/2	2/2	NA

- Role of higher potency CpAM on increasing chance of success of off-treatment/partial cure/functional cure need to be investigated

MacQuillan G et al AASDL 2023: OS47

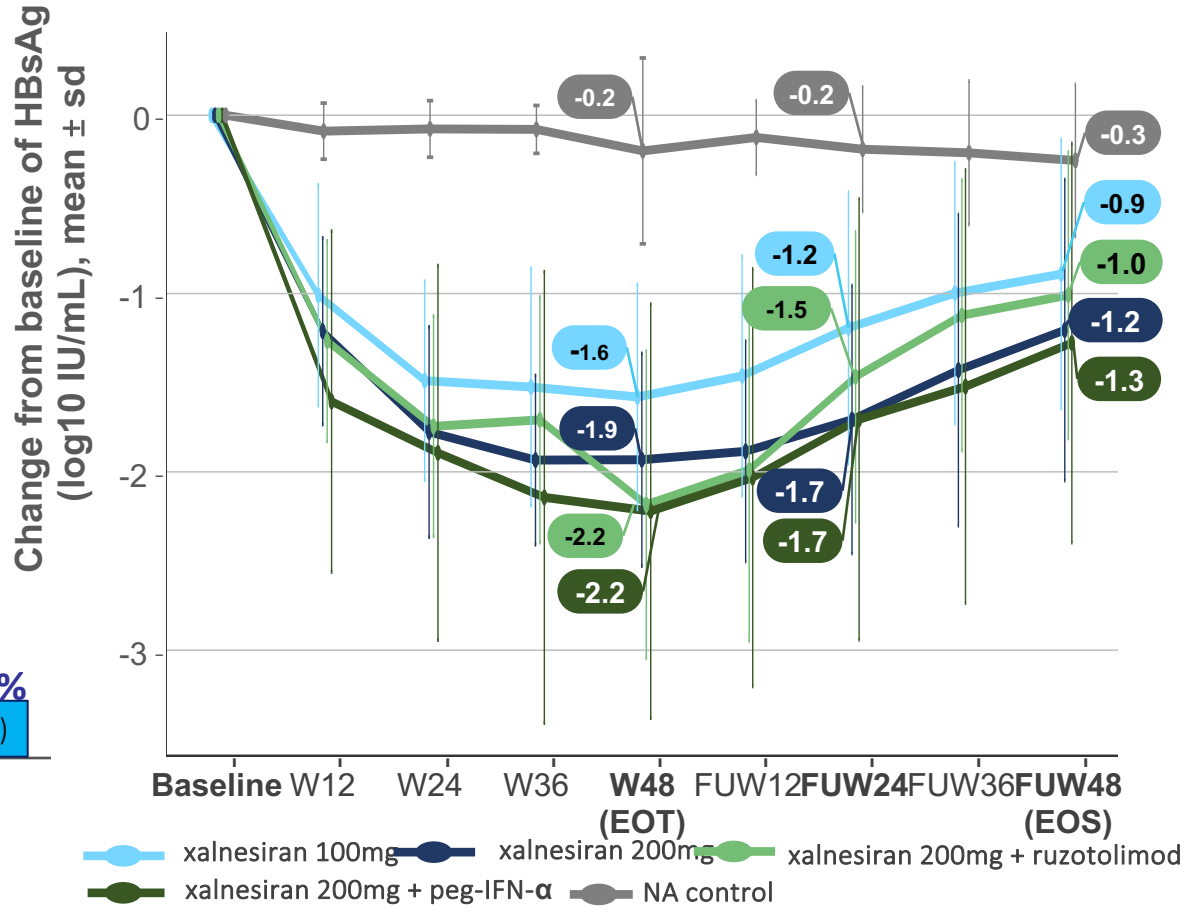
PIRANGA: partial sustained FC 48 weeks off-treatment responses among virologically-suppressed CHB pts treated for 48 weeks with xalnesiran (siRNA) combination therapies + immunomodulator ruzotolimod (TLR7 agonist) or PegIFN

HBsAg loss only in patients with baseline HBsAg<1000 IU/ml



HBsAg seroconversion at Wk48

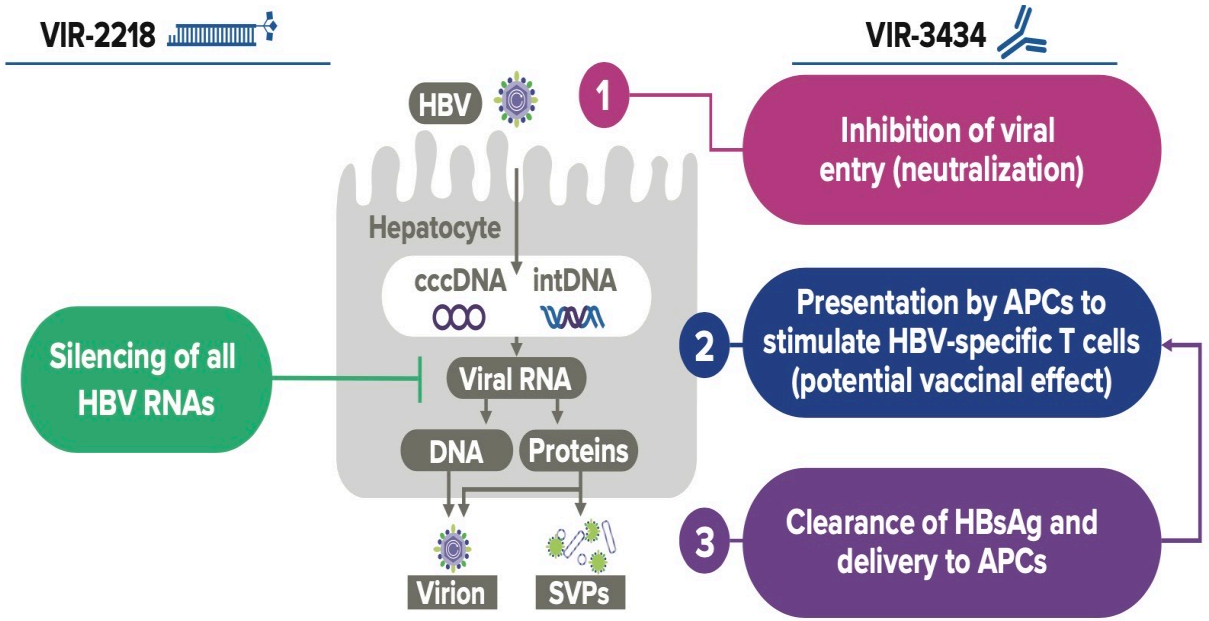
- N=5 xalnesiran +PegIFN
- N=4 xalnesiran+ ruzotolimob
- N=0 xalnesiran 100 mg



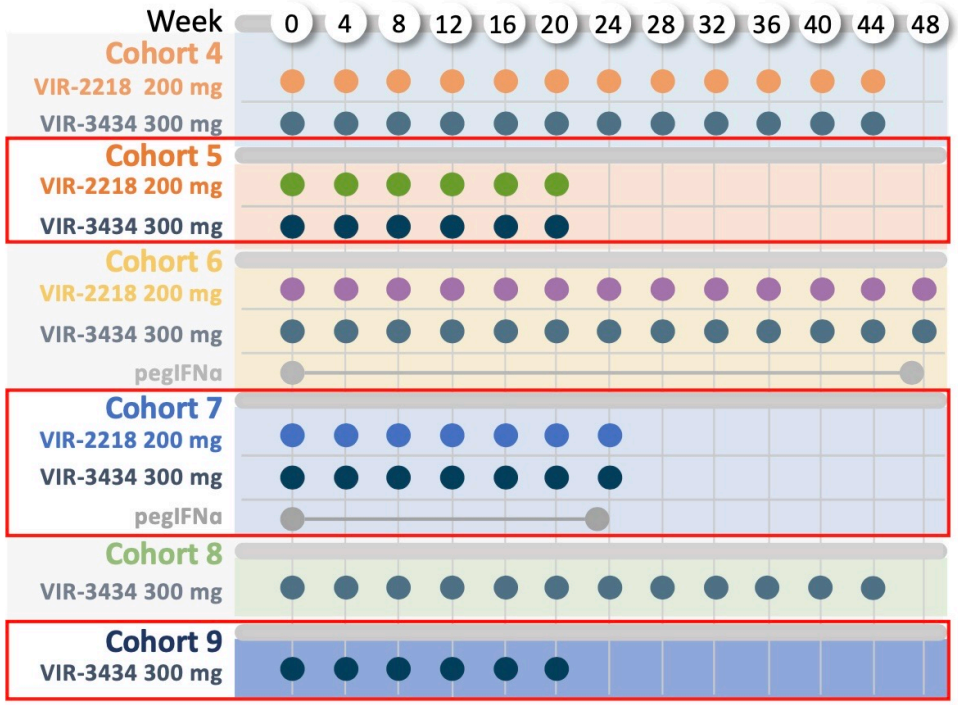
- Durability of HBsAg loss between EOT and FUW48 was observed in 56% of participants treated with xalnesiran and peg-IFN-α, with seroconversion being a potential factor associated with maintenance

Asselah T. et al., EASL 2024 OS-030

MARCH STUDY Part B: VIR-2218 (siRNA) and VIR-3434 (Mab) + PegIFN among virologically-suppressed CHB patients: EOT and 12 weeks post EOT



Study design (MARCH Part B)

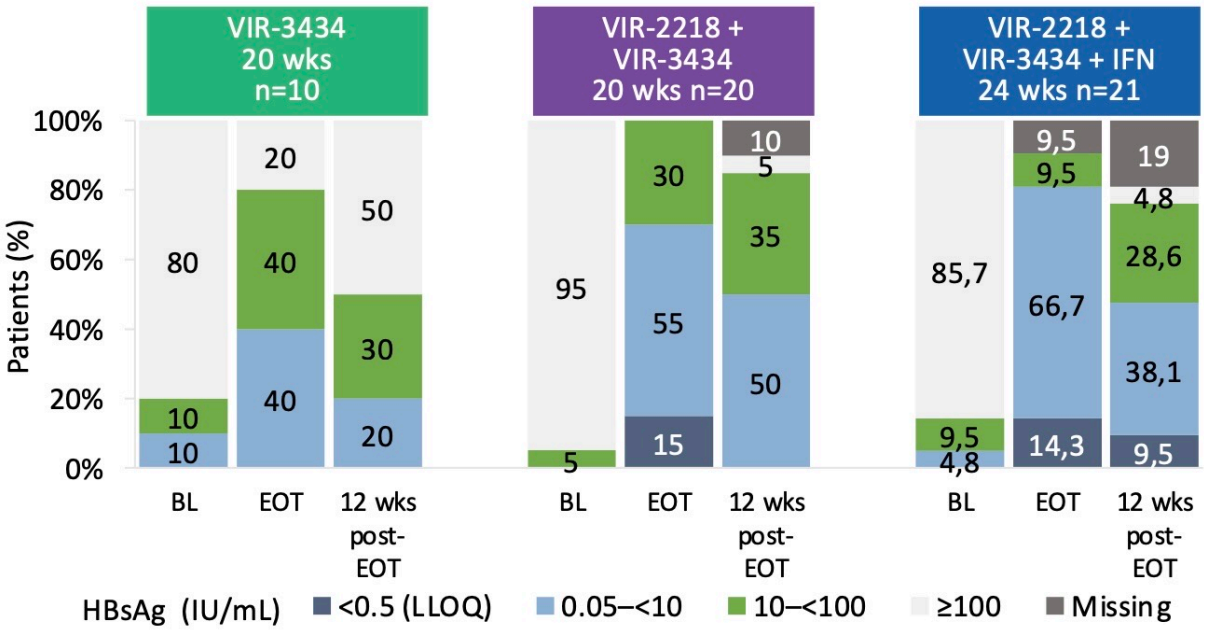


- Cohorts 5, 7, and 9 reported here
- **Primary endpoints**: Safety, HBsAg loss at EOT

Gane E. et al. , AASLD 2023, Abs. 5013 updated

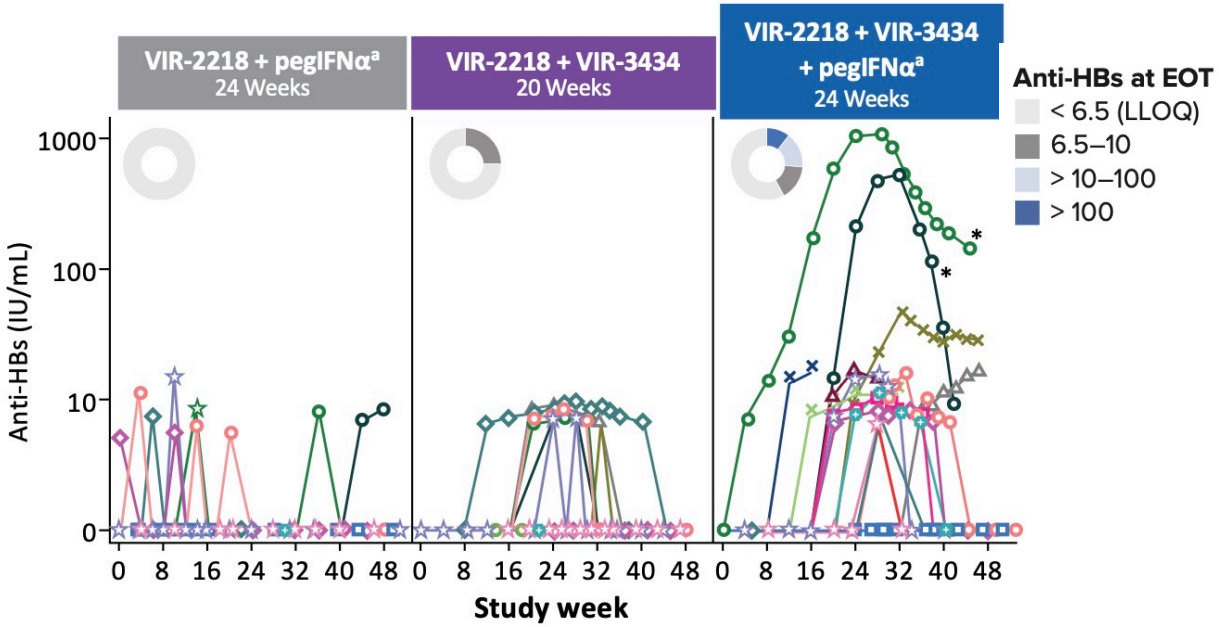
MARCH STUDY Part B: VIR-2218 (siRNA) and VIR-3434 (Mab) + PegIFN among virologically-suppressed CHB patients: EOT and 12 weeks post EOT

HBsAg distribution at BL, EOT and 12 weeks post-EOT



- At EOT: HBsAg loss in
  - VIR-3434: 0% (0/10)
  - VIR-2218 + VIR-3434: 15% (3/20); 0 at 12 wks post-EOT
  - VIR-2218 + VIR-3434 + pegIFN: 14.3% (3/21); 2 maintained response
- All HBsAg loss in HBeAg neg patients with BL HBsAg <3000 IU/mL
- HBsAg <10 IU/mL at EOT in 40%, 70%, and 81%
- In HBeAg pos patients 0/3, 1/5, 2/9 HBeAg neg at EOT

Anti-HBs concentrations by cohort



- Anti-HBs concentration >10 IU/mL in 11/21 (52%) at EOT in VIR-2218 + VIR-3434 + pegIFN cohort
  - Comparison 2/18 (11%) in earlier cohort of VIR-2218 + pegIFN 24 weeks
  - Highest anti-HBs levels in the 2 patients who maintained HBsAg loss post-EOT

Gane E. et al. , AASLD 2023, Abs. 5013 updated

MARCH STUDY Part B: VIR-2218 (siRNA) and VIR-3434 (Mab) + PegIFN among virologically-suppressed CHB patients: EOT and 12 weeks post EOT

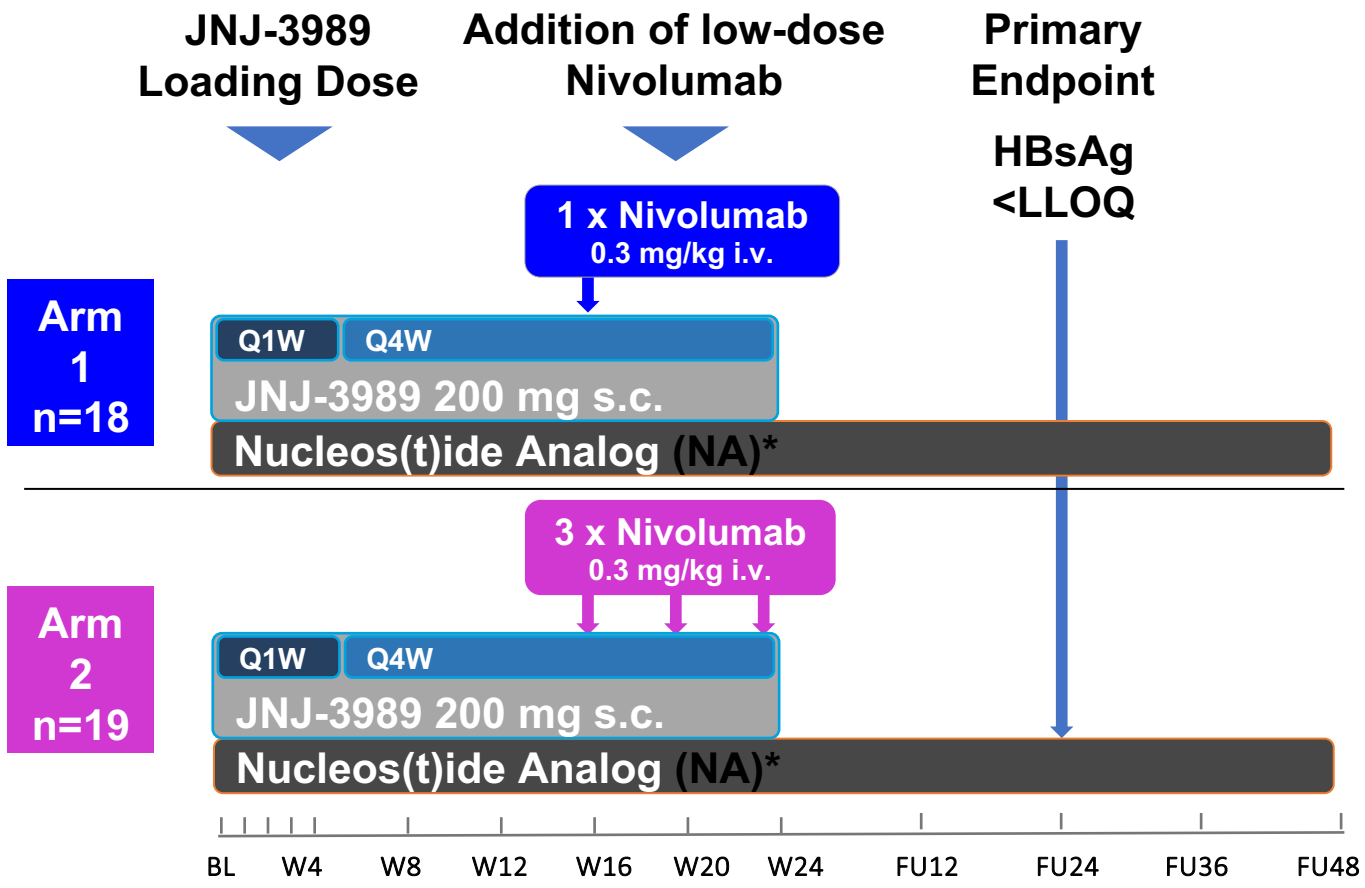
Rates of HBsAg loss at EOT and 12weeks post EOT

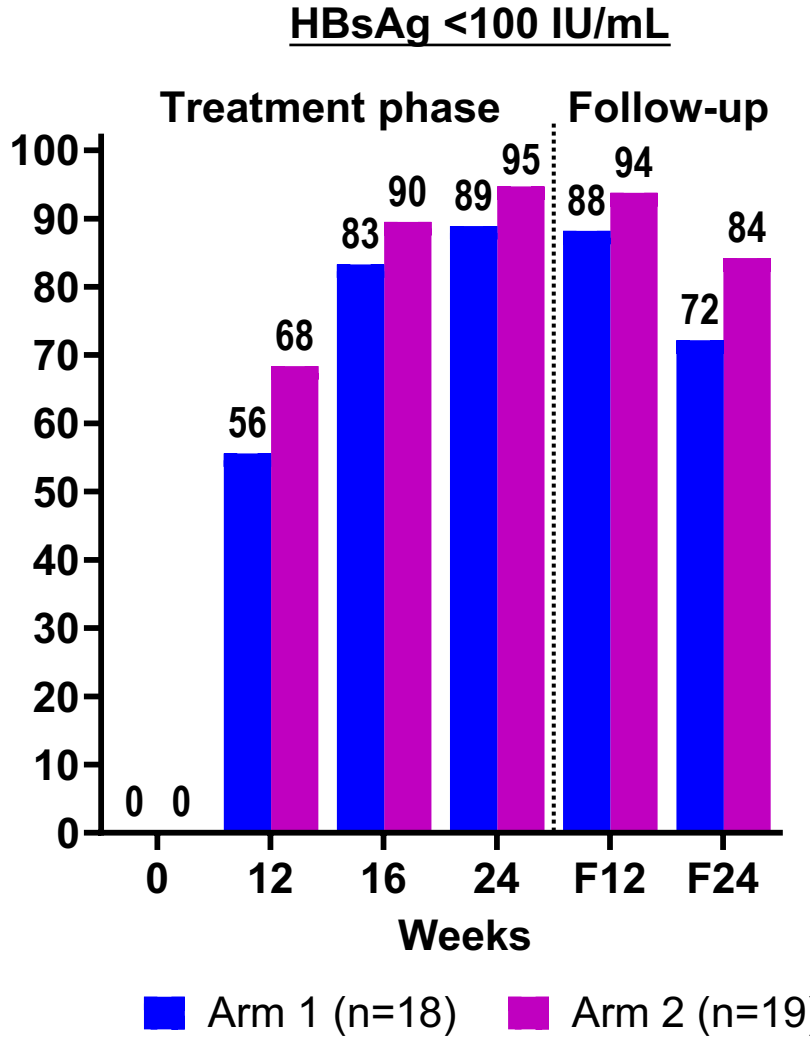
	Previously reported			MARCH part B			Previously Reported
	VIR-2218 + VIR-3434 12 weeks (n = 19)	**VIR-2218 + Peg-IFN 12 weeks** (n = 5)	**VIR-2218 + Peg-IFN 24 weeks** (n = 18)	**VIR-3434 20 weeks** (n = 10)	**VIR-2218 + VIR-3434 20 weeks** (n = 20)	**VIR-2218 +VIR-3434 +Peg-IFN 24 weeks** (n = 21)	**VIR-2218 + Peg-IFN 48 weeks** (n = 13)
At EOT	0	0	1 (5,6 %)	0	3 (15 %)	**3 (14,3 %)**	4 (30,8 %)
Baseline HBsAg < 3000 IU/ml	0/17	0/17	1/9 (11,1 %)	0/8	3/13 (23,1 %)	3/16 (18,8 %)	2/6 (33,3 %)
Baseline HBsAg ≥ 3000 IU/ml	0/2	0/3	0/9	0/2	0/7	0/5	2/7 (28,6 %)
12 weeks post EOT	0	0	0	0	0	**2/21 (9,5 %)**	0

The virologic and immunologic outcomes observed in this study strongly support the potential of 48-week regimens of VIR-2218 +VIR-3434, with or without PEG-IFNα, to result in meaningful rates of functional cure

Gane E. et al. , AASLD 2023, Abs. 5013 updated

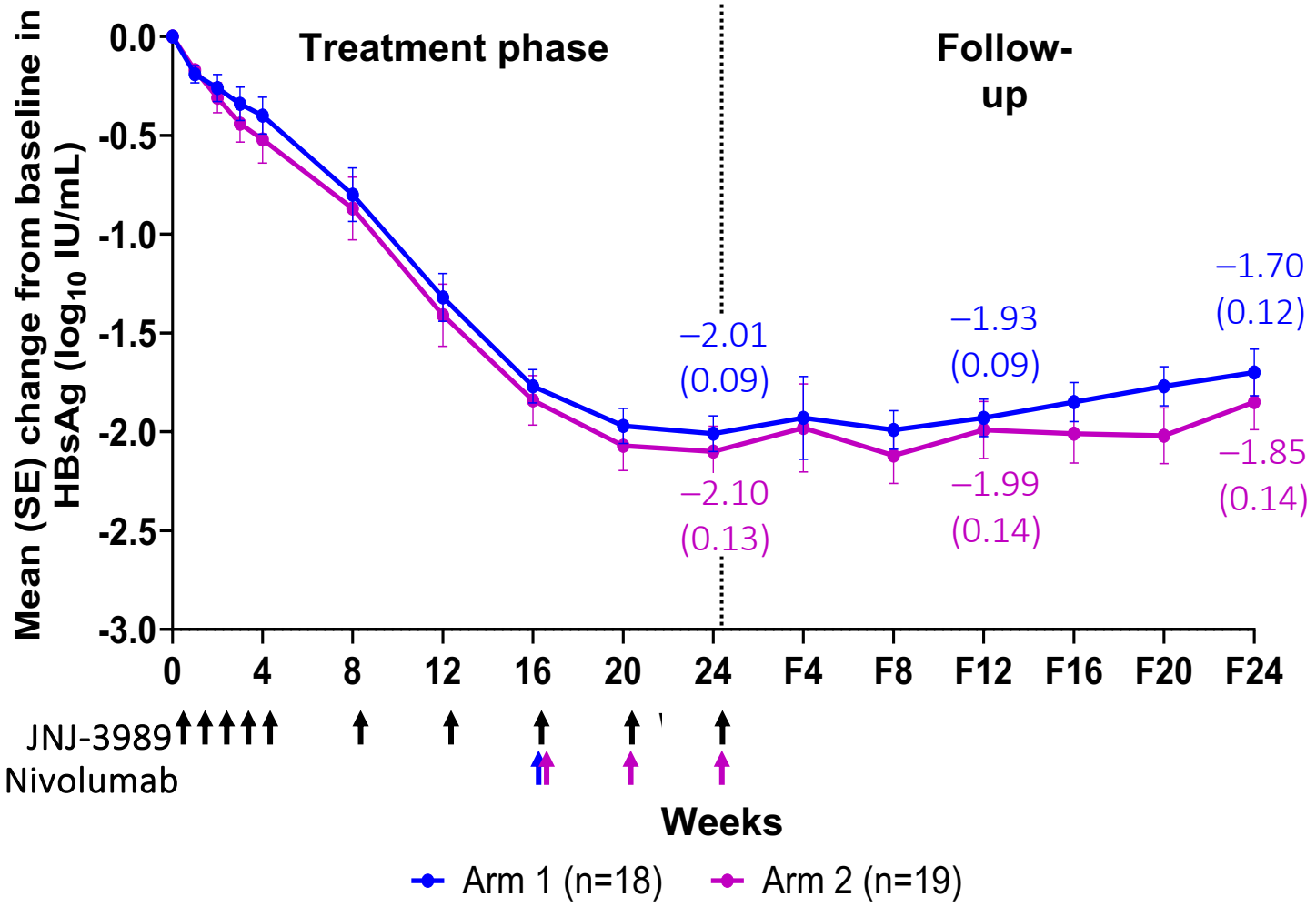
Octopus-1 : JNJ-73763989 (siRNA) in combination with NUC and Low dose Nivolumab (PD-1 inhibitor) among virologically-suppressed HBeAg-negative CHB patients for 24 weeks





Asselah T et al EASL 2024: OS 033

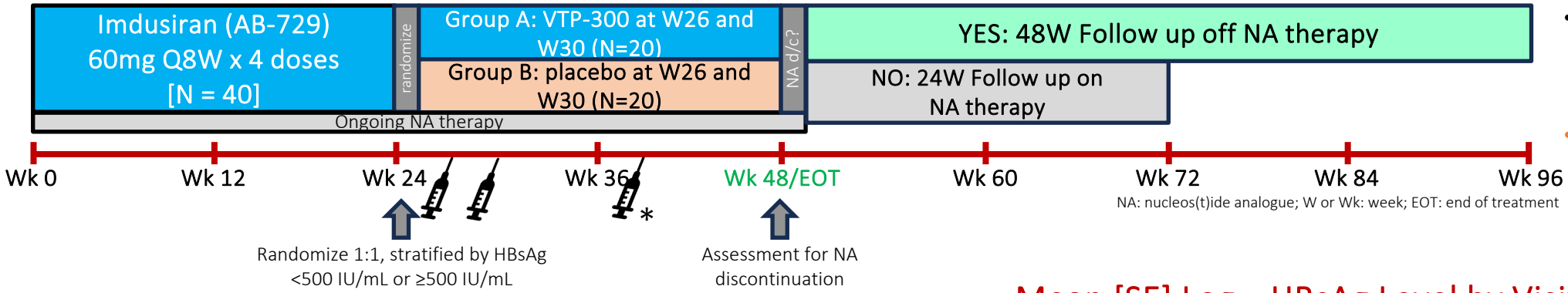
Octopus-1 : JNJ-73763989 (siRNA) in combination with NUC and Low dose Nivolumab (PD-1 inhibitor) among virologically-suppressed HBeAg-negative CHB patients for 24 weeks



- At FU Week 24
  - No participant met the Primary Endpoint of HBsAg <LLOQ
  - A high proportion of patients maintain HBsAg <100 IU/mL
  - However, two events of temporary TSH suppression after nivolumab infusions together with no clear benefit of its addition to efficacy led to a protocol amendment to not further expose patients to nivolumab in this study

Asselah T et al EASL 2024: OS 033

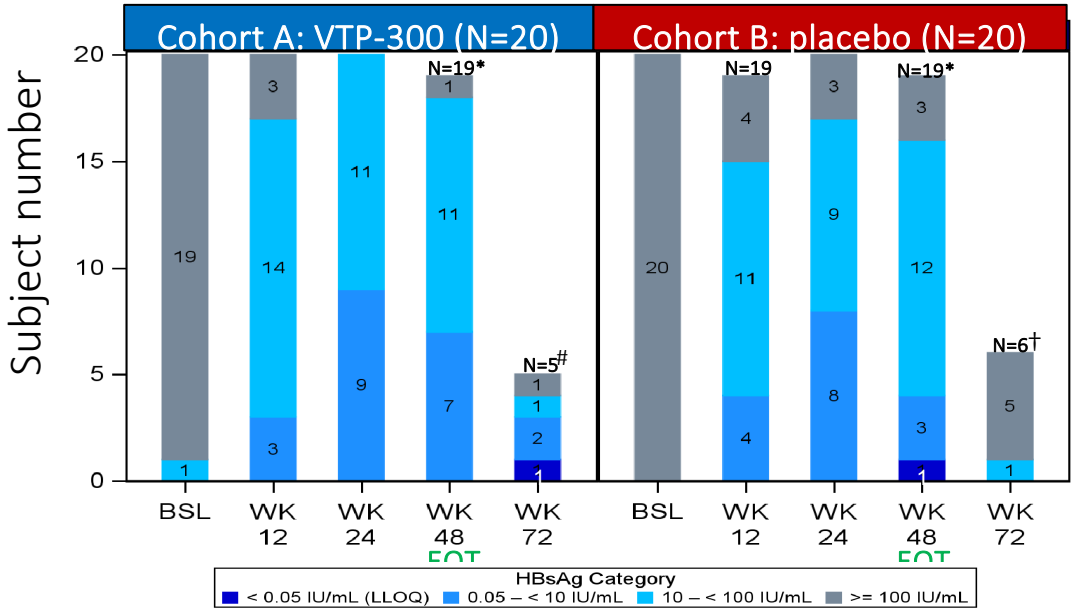
IM Prove-2: Imdusiran (AB-729 siRNA) administered every 8 weeks for 24 weeks followed by the immunotherapeutic VTP-300 (Vaccine) maintains lower HBV surface antigen levels in NA-suppressed CHB subjects than 24 weeks of imdusiran alone



NA: nucleos(t)ide analogue; W or Wk: week; EOT: end of treatment

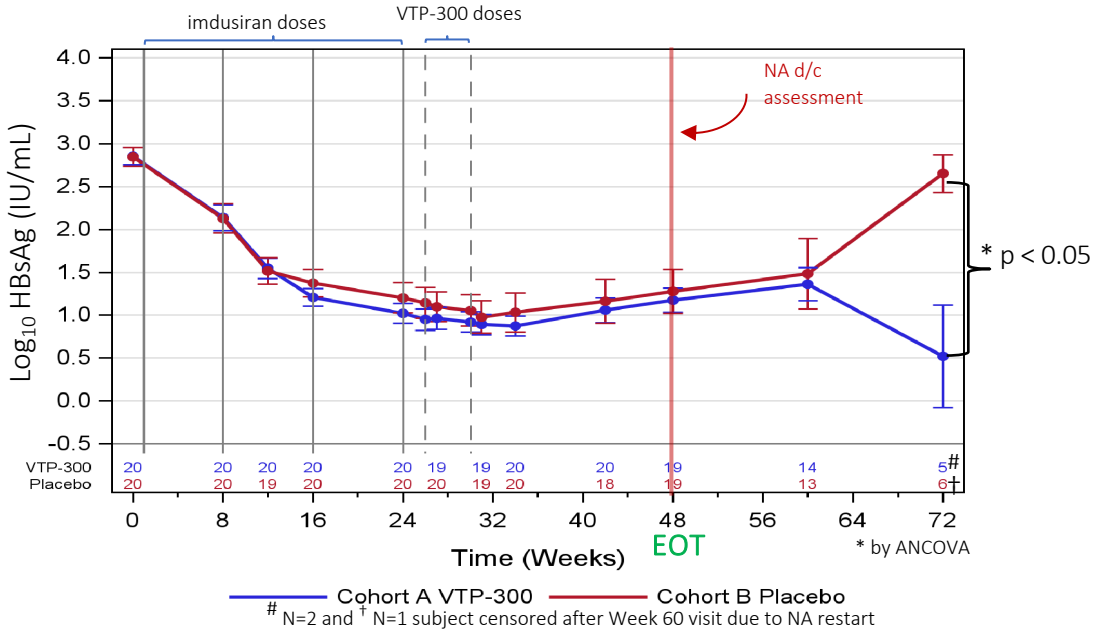
- Optional 2nd MVA-HBV boost/placebo dose at Week 38:
  - Additional ≥0.5 $\log_{10}$ HBsAg decline between Weeks 26 and 34
- NA discontinuation occurred after Week 48/EOT visit if all criteria were met:
  - HBV DNA < LLOQ
  - HBeAg negative
  - HBsAg < 100 IU/mL
  - ALT <2 × ULN

HBsAg Thresholds Achieved by Visit



BSL=baseline; WK=week; EOT=end of treatment; * 2 subjects did not reach timepoint by datacut; # N=2 and † N=1 subject censored after Week 60 visit due to NA restart

Mean [SE] $\log_{10}$ HBsAg Level by Visit



N=2 and † N=1 subject censored after Week 60 visit due to NA restart

Agarwal K, et al., EASL 2024, Abs. OS-031

IM Prove-2: Imdusiran (AB-729 siRNA) administered every 8 weeks for 24 weeks followed by the immunotherapeutic VTP-300 (Vaccine) maintains lower HBV surface antigen levels in NA-suppressed CHB subjects than 24 weeks of imdusiran alone

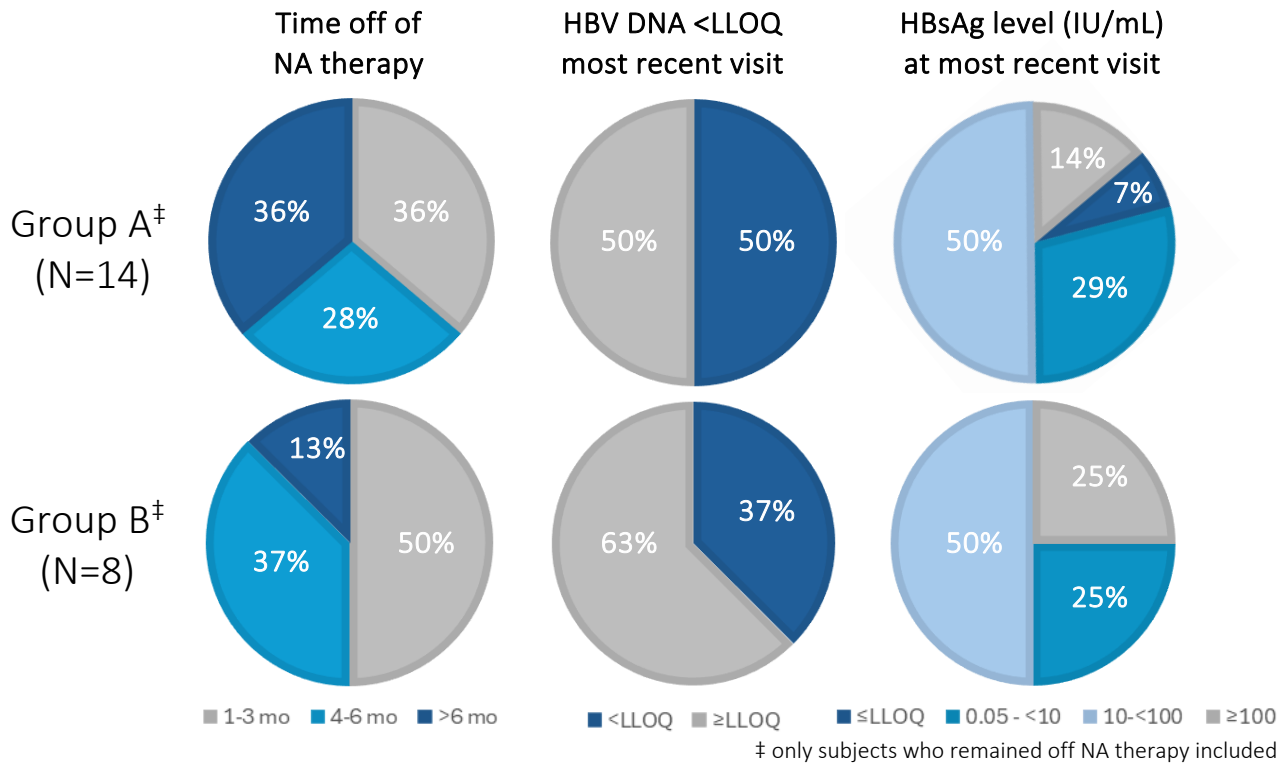
More subjects in Group A/VTP-300 stopped NA treatment

NA Discontinuation Summary N, (%)	Group A VTP-300	Group B placebo
Stopped NA treatment after Week 48[#] (HBV DNA <LLOQ, HBeAg-, ALT <2x ULN, HBsAg <100 IU/mL)	16/19 (84%)	10/19 (53%)
Did not meet NA stopping criteria: HBeAg+ HBsAg > 100 IU/mL	3/19 (16%) 2/3 1/3	9/19 (47%) 9/9* 3/9*
Met NA restart criteria[†]	2/16 (13%)	2/10 (20%)

[#] 2 subjects (1 in each Group) had not reached Week 48 timepoint as of data cut date

* 3 subjects were both HBeAg+ and had HBsAg >100 IU/mL

[†] All NA restarts were due to confirmed HBV DNA >20,000 IU/mL **without** ALT >2x ULN



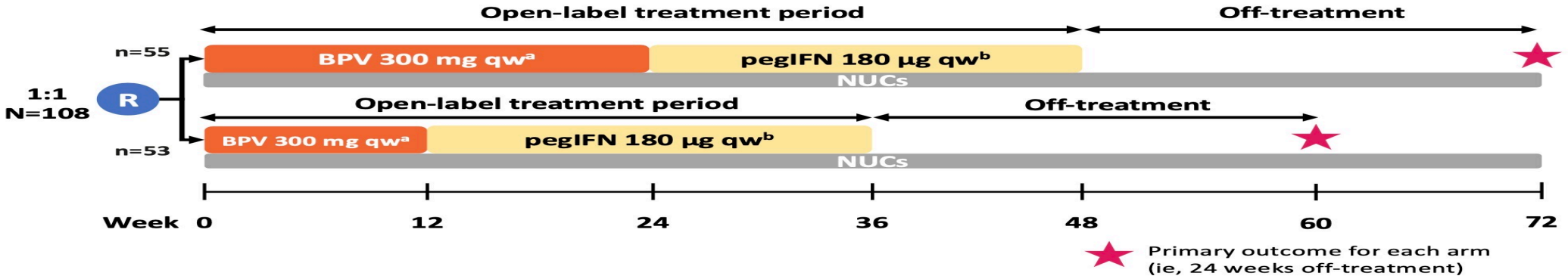
‡ only subjects who remained off NA therapy included

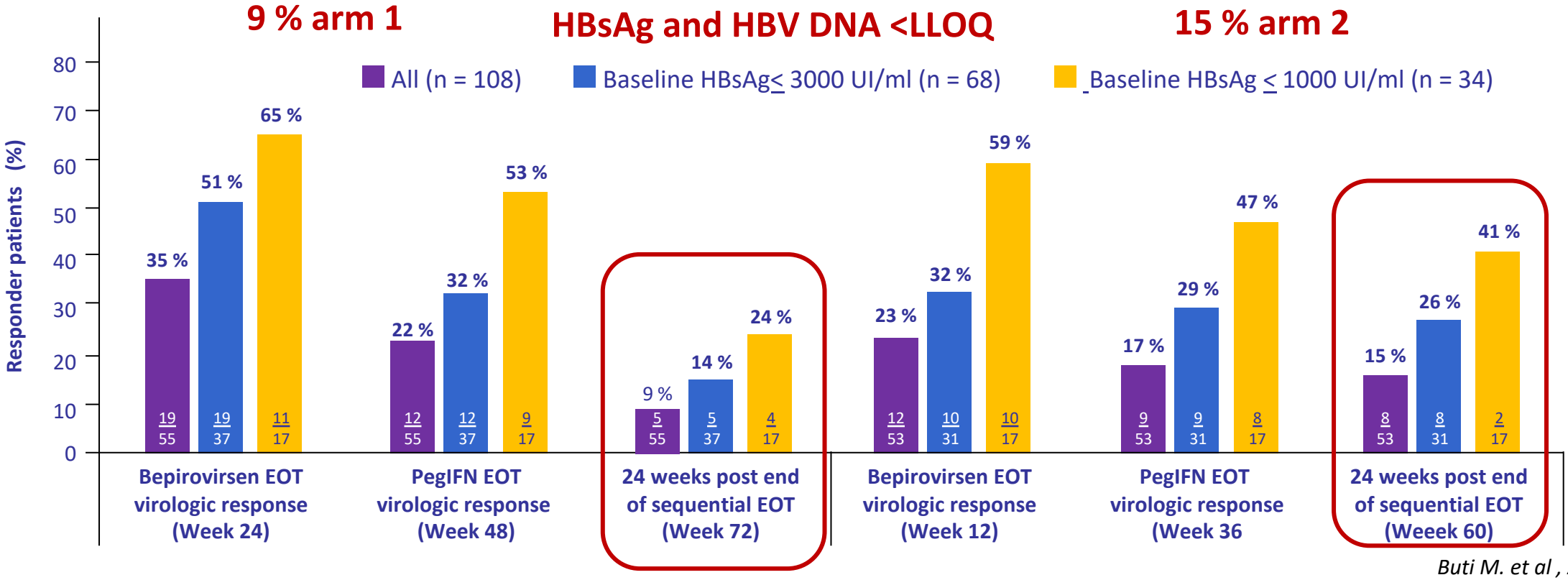
Agarwal K, et al., EASL 2024, Abs. OS-031

ASO development

- In monotherapy or add-on with NUCs (on going phase III)
- With PegIFN

B-together: PegIFN following bepirovirsen (ASO) treatment in virologicaly-suppressed patients

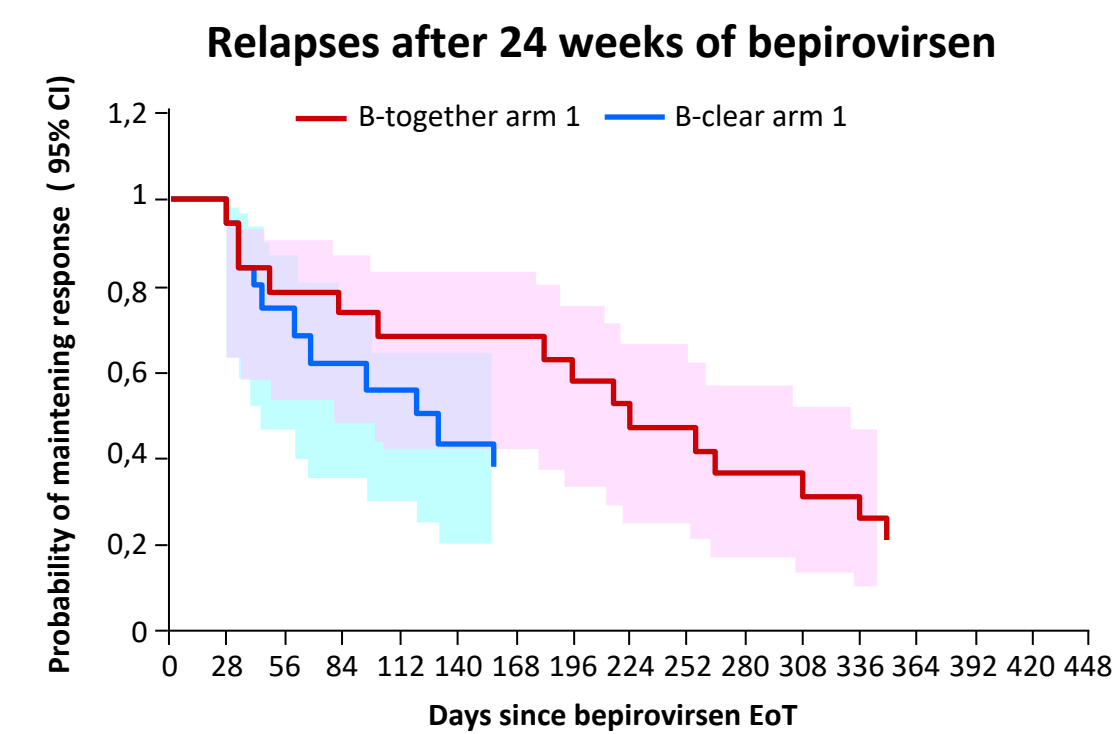


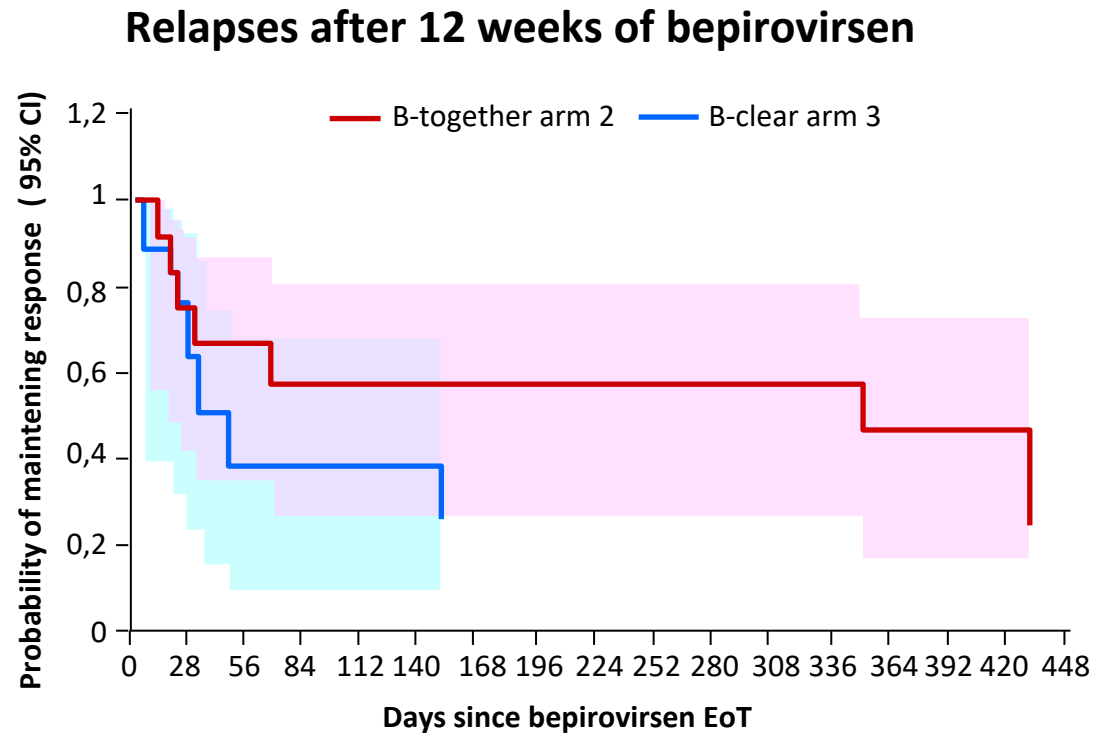


Buti M. et al , AASLD 2023, Abs. OS49

B-together: PegIFN following bepirovirsen (ASO) treatment in virologicaly-suppressed patients

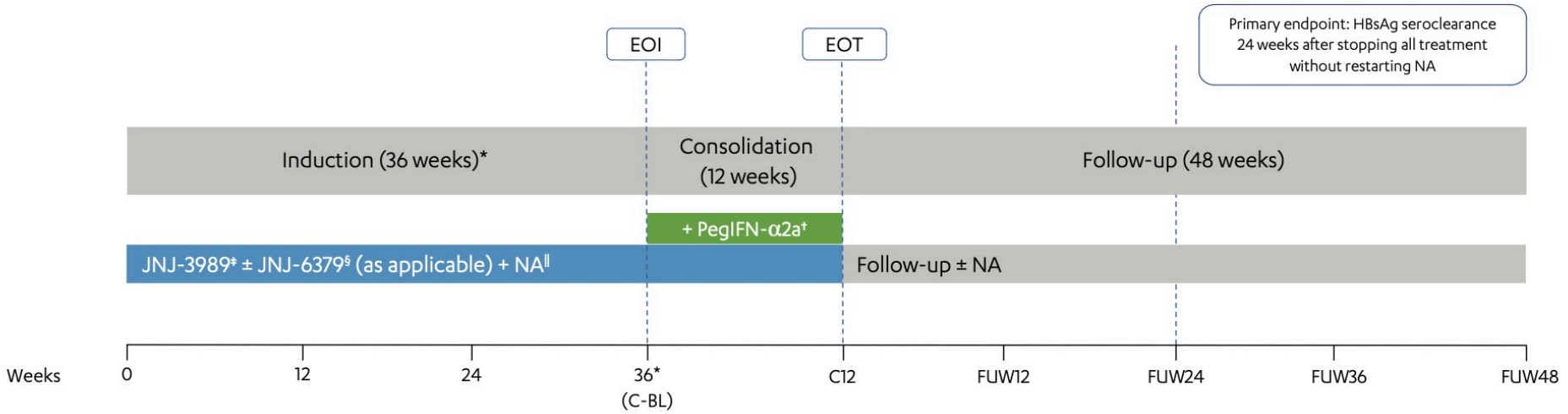
Sequential treatment of bepirovrisen followed by PegIFN reduced relapses rates compared with B-clear



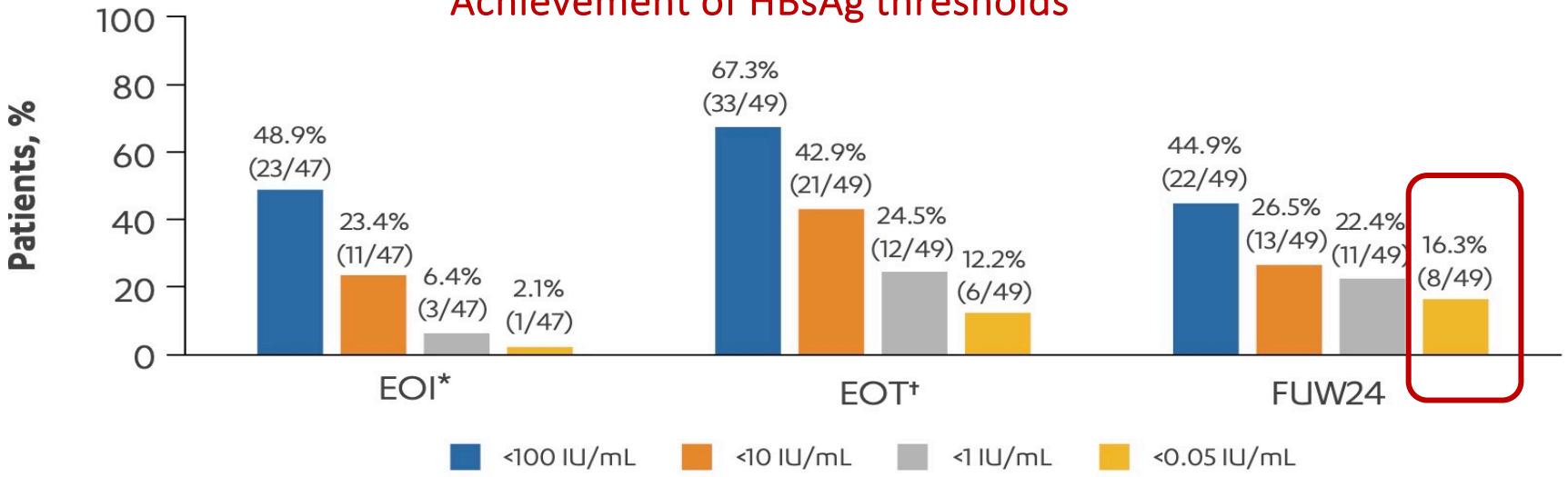


Buti M. et al , AASLD 2023, Abs. OS49

REEF-IT: reduction in HBsAg among "immune –tolerant"patients with CHB treated with JNJ-3839 (siRNA), JNJ -6379 (CAM-E) and NUCs with pegIFN added



Achievement of HBsAg thresholds

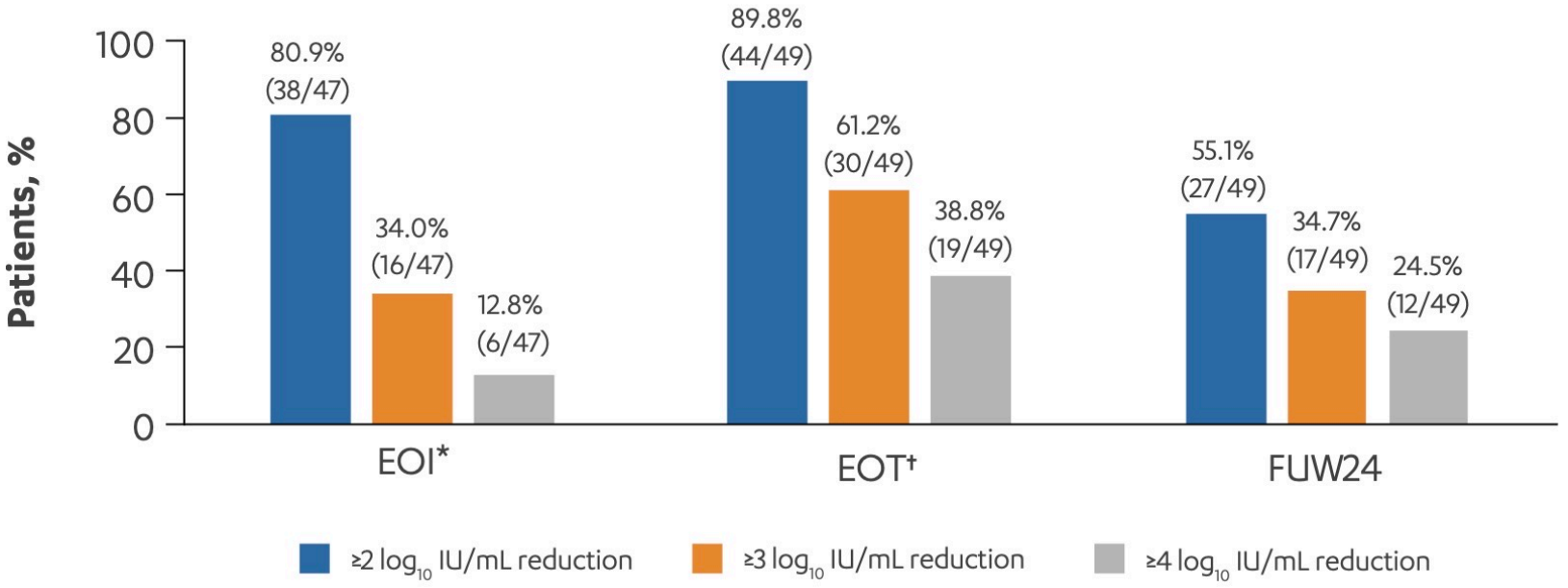


Profound HBV DNA reductions were observed; 66.7% of patients achieved HBV DNA <LLOQ and 91.7% achieved HBV DNA <100 IU/mL by FUW24

Kennedy P et al., AASLD 2023, Abs. 1468 updated

REEF-IT: reduction in HBsAg among “immune –tolerant”patients with CHB treated with JNJ-3839 (siRNA), JNJ -6379 (CAM-E) and NUCs with pegIFN added

Achievement of reduction from baseline HBsAg thresholds



HBsAg seroclearance was achieved by11 (20%) patients, 6 of whom remained negativeat the last available time point,
and HBeAgseroclearance was achieved by 15 (28%) patients, 11 of whom remained negative at the last available time point

HBsAg undetectability can be achieved in immune tolerant patients

Kennedy P et al., AASLD 2023, Abs. 1468 updated

Conclusions :
HBsAg loss is now more achievable

- **Capsid assembly modulators** are still in the game
- **SiRNA** plays a key role in future combination therapies
  - With direct acting antivirals
  - With immune modulators
  - With therapeutic vaccines
- **Bepirovirsen** is still in development with PegIFN and other direct acting antivirals
- **PegIFN** may plays a key role in combination to enhance and sustain virologic response
- HBsAg loss is possible in immune tolerant patients with quadruple combination therapy
- Overall substantial advance are being seen in clinical trials and **functional cure seems more achievable, however ideal combinations are still an open question**