La cura de la Hepatitis por el VHB una meta alcanzable en los próximos años.

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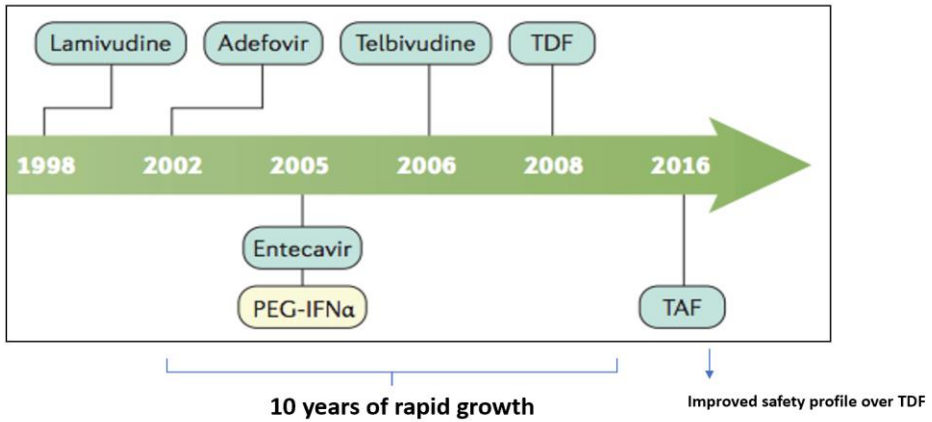
Disclosures

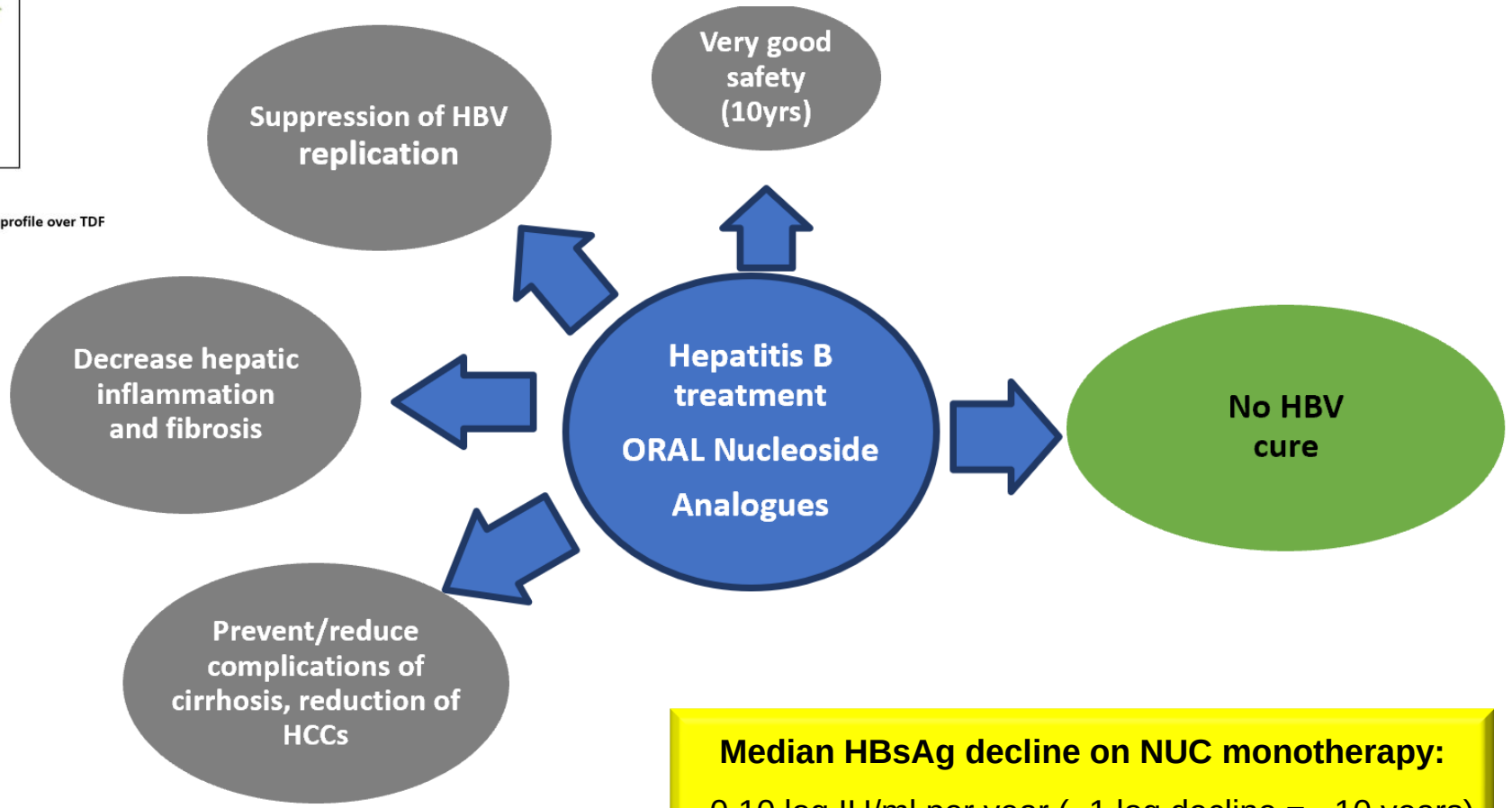
- MB speaker and/or Advisor Gilead, Abbvie, Altimmune, GSK, Janssen and Assembly

JM 51 años

- Hepatitis Crónica B HBeAg negativo diagnosticada en 2003
- Biopsia Hepatica : Hepatitis Cronica con F4 (Ishak Fibrosis score)
- Inicio Tratamiento con TDF en Feb 2004
- Desde Dic 2004, ALT normales, DNA-VHB indetectable, HBsAg 450 IU/Ml
- Inclusion studio NUCs+siRNA 48 semanas
- Fin tratHBsAg negativo
- 24 semanas tras finalizar el studio persiste con HBsAg negativo

Evolution and Current Treatment for HBV

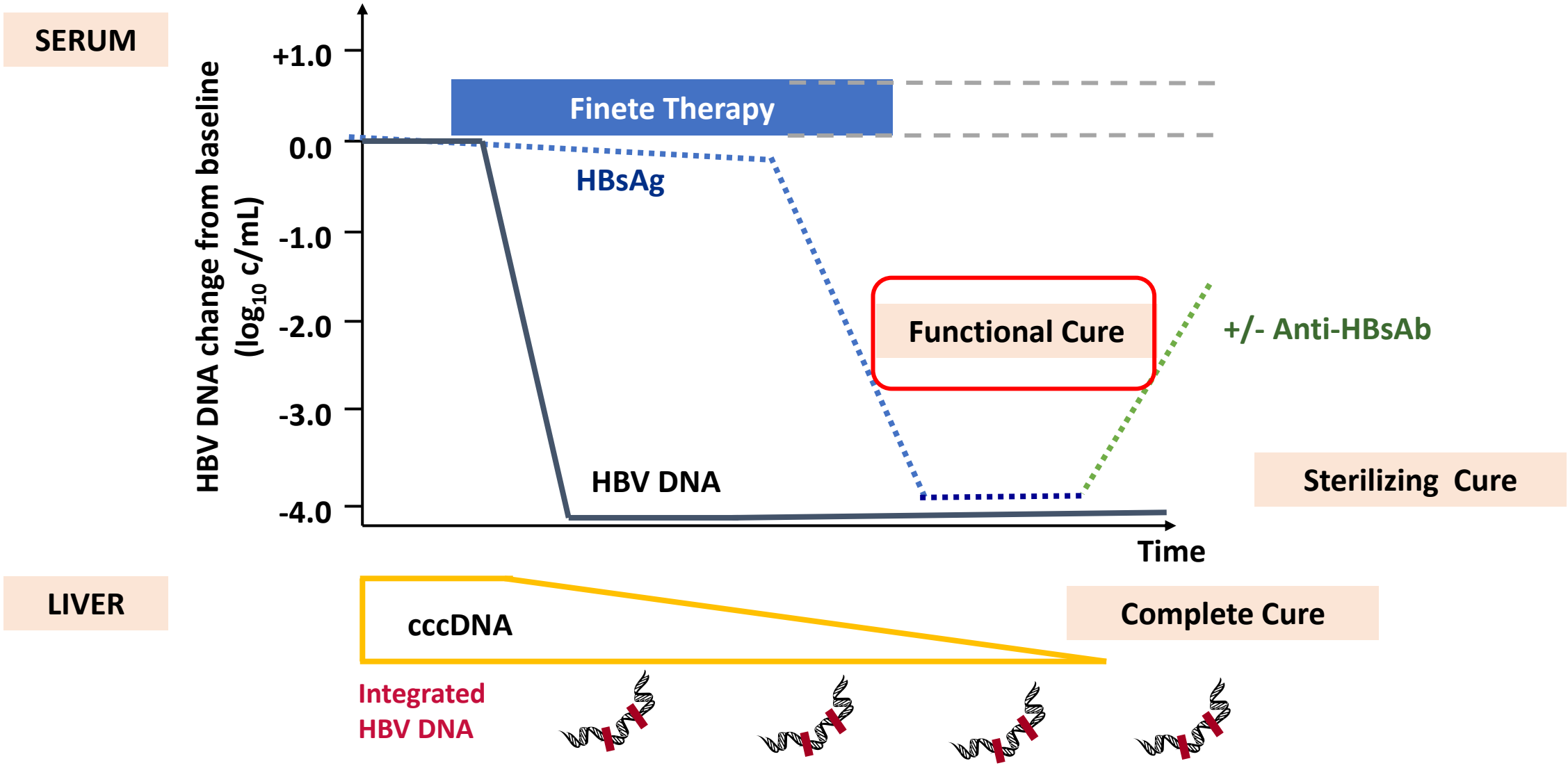




Median HBsAg decline on NUC monotherapy:

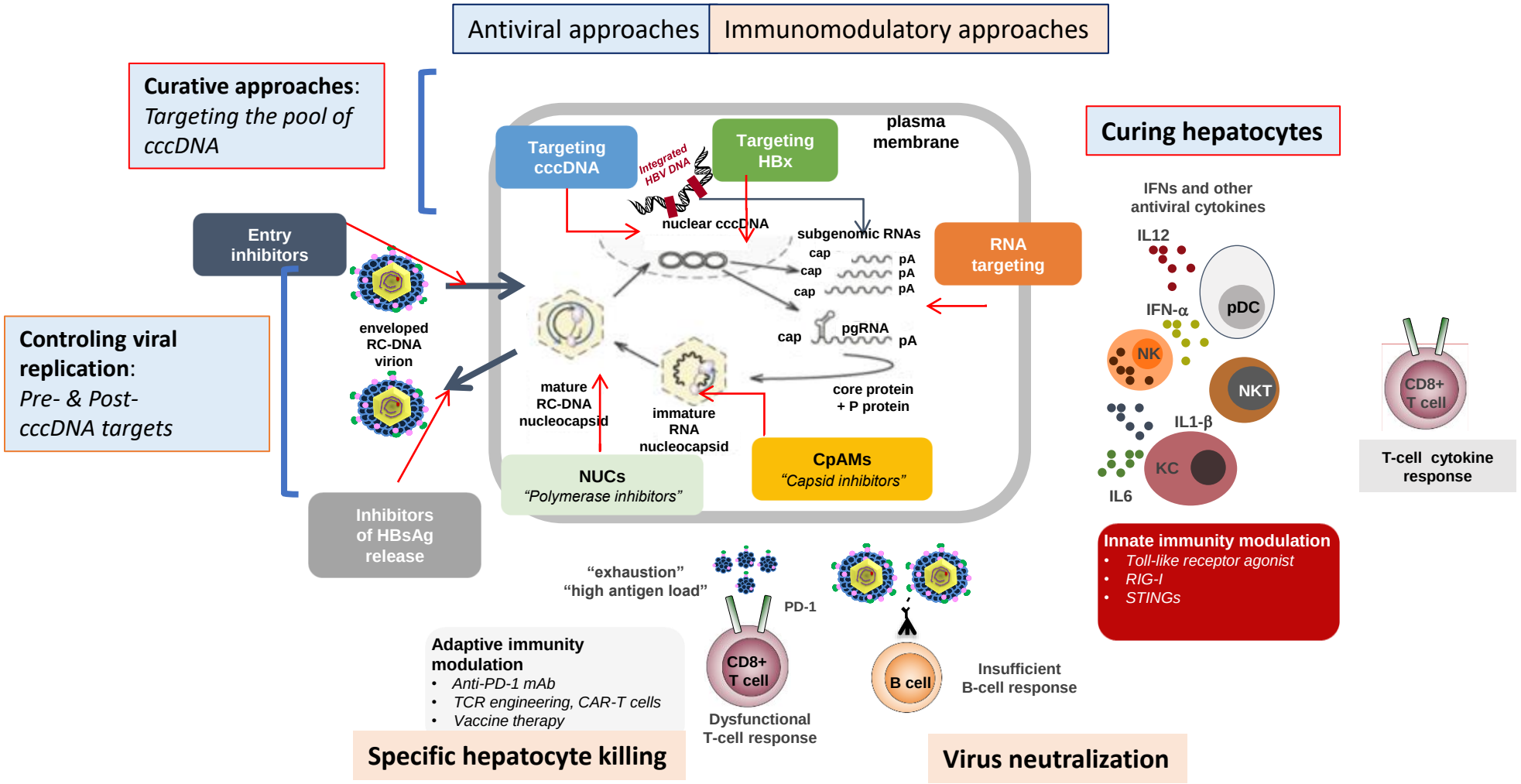
~0.10 log IU/ml per year (~1 log decline = ~10 years)

Towards a functional cure of HBV infection



Adapted from Testoni et al. Semin Liver Dis. 2017; Cornberg et al J Hepatol 2019

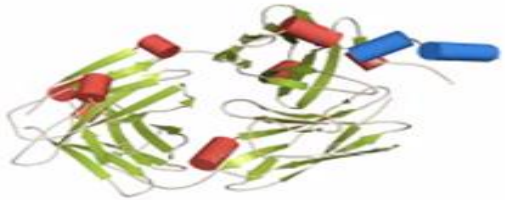
Novel targets and drug pipeline



2023 Pipeline >50 drugs in preclinical, phase 1-2 clinical study

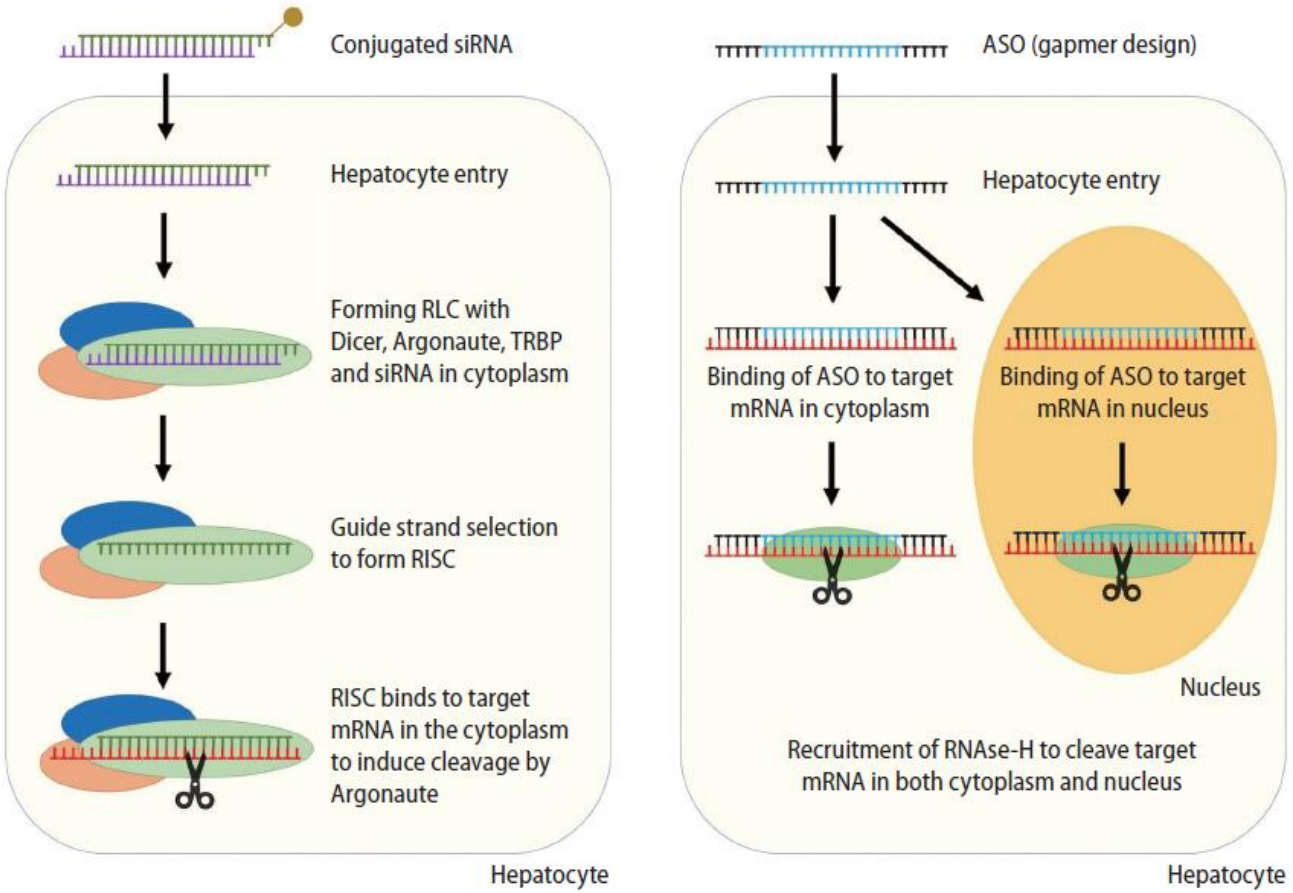
Revill & Zoulim, et al, Lancet Gastroenterol Hepatol. 2019; Fanning & Zoulim, et al, Nat Rev Drug Discov. 2019

Targets for Combination of New Therapies



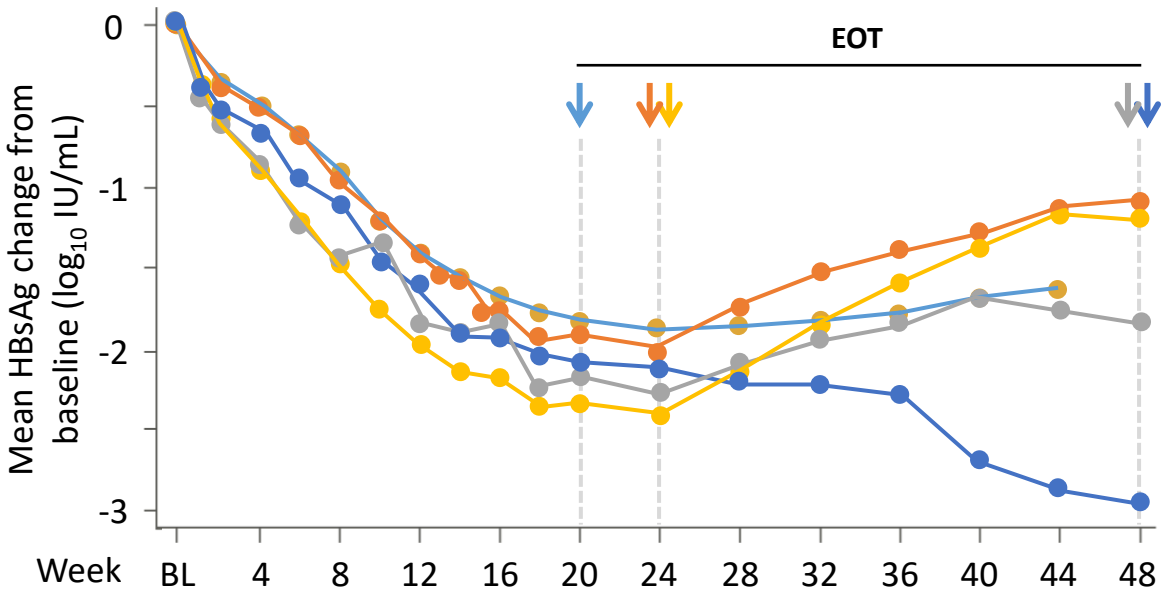
Replication inhibition	Antigen reduction	Immune stimulation	
Capsid Assembly Modulators (CAMs)	**Small interference RNA (sIRNA)**	**TLR-8 agonist**	**Therapeutic Vaccines**
Nucleos(t)ide Analogues	**Antisense Oligonucleotide (ASO)**	**TLR-7 agonist**	**Check Point inhibitors**
	Nucleic Acid Polymers (NAPs) S-antigen transport – inhibiting oligonucleotide polymers (STOPs)	**PDL1 inhibitors**	

Mechanism of action siRNA vs ASO



Phase 2 trial: Preliminary 48-week safety and efficacy data of siRNA VIR-2218 alone and in combination with pegIFNα in patients with chronic HBV

HBsAg through Week 48



Mean ±SD (n)	HBsAg Mean change from baseline (log_{10} IU/mL)		
	Week 24	Week 36	Week 48
VIR-2218 × 6	–1.9 ±0.25 (15)	–1.8 ±0.39 (15)	–1.6 ±0.42 (15)[a]
VIR-2218 × 6 lead-in + pegIFNα × 12	–2.0 ±0.69 (15)	–1.4 ±0.80 (15)	–1.1 ±0.83 (15)
VIR-2218 × 6 + pegIFNα × 24	–2.4 ±0.71 (16)	–1.6 ±0.66 (16)	–1.2 ±0.54 (17)
VIR-2218 × 6 + pegIFNα × ≤48	–2.3 ±0.86 (16)	–1.8 ±1.62 (16)	–1.8 ±1.71 (16)
VIR-2218 × ≤13 + pegIFNα × ≤44	–2.1 ±0.62 (13)	–2.3 ±0.81 (13)	–2.9 ±1.36 (13)

HBsAg seroclearance

n (%)	VIR-2218 × 6 (n=15)	VIR-2218 × 6 lead-in + pegIFNα × 12 (n=15)	VIR-2218 × 6 + pegIFNα × 24 (n=5)	VIR-2218 × 6 + pegIFNα × ≤48 (n=18)	VIR-2218 × ≤13 + pegIFNα × ≤44 (n=13)
At any time up to Week 48	0	1 (7)	1 (6)	4 (22)	4 (31)
At Week 48	0	1 (7)	0	3 (17)	4 (31)
With anti-HBs (>10 mIU/mL) at Week 48	0	1 (7)	0	3 (17)	4 (31)

[a]Week 44 for cohort A as Week 48 visit was not required

Yuen M-F, et al. AASLD 2022. Oral #19. Sponsored by Vir Biotechnology, Inc.

Efficacy and safety of bepirovirsen in patients with CHB: Interim results from the randomized Phase 2b B-Clear study

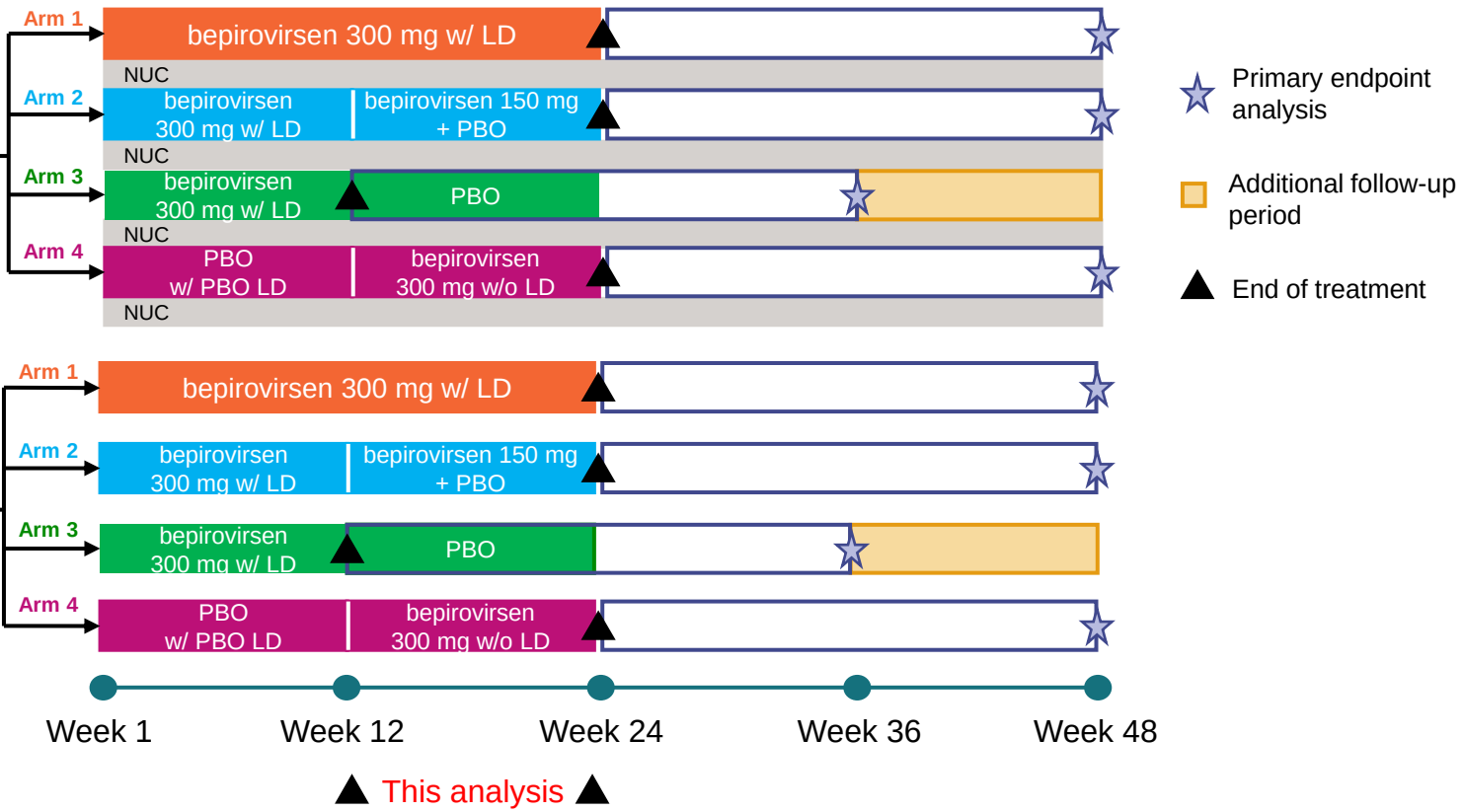
Inclusion criteria
- Chronic HBV infection ≥6 months
- ALT ≤2xULN
- HBV DNA <90 IU/mL
- HBsAg >100 IU/mL

On-stable NUC therapy n=227

Inclusion criteria
- Chronic HBV infection ≥6 months
- ALT <3xULN
- HBV DNA >2000 IU/mL
- HBsAg >100 IU/mL

Not currently on NUC therapy n=230

Stratification
- HBeAg positive/negative
- HBsAg ≤3 $\log_{10}$ IU/mL or >3 $\log_{10}$ IU/mL



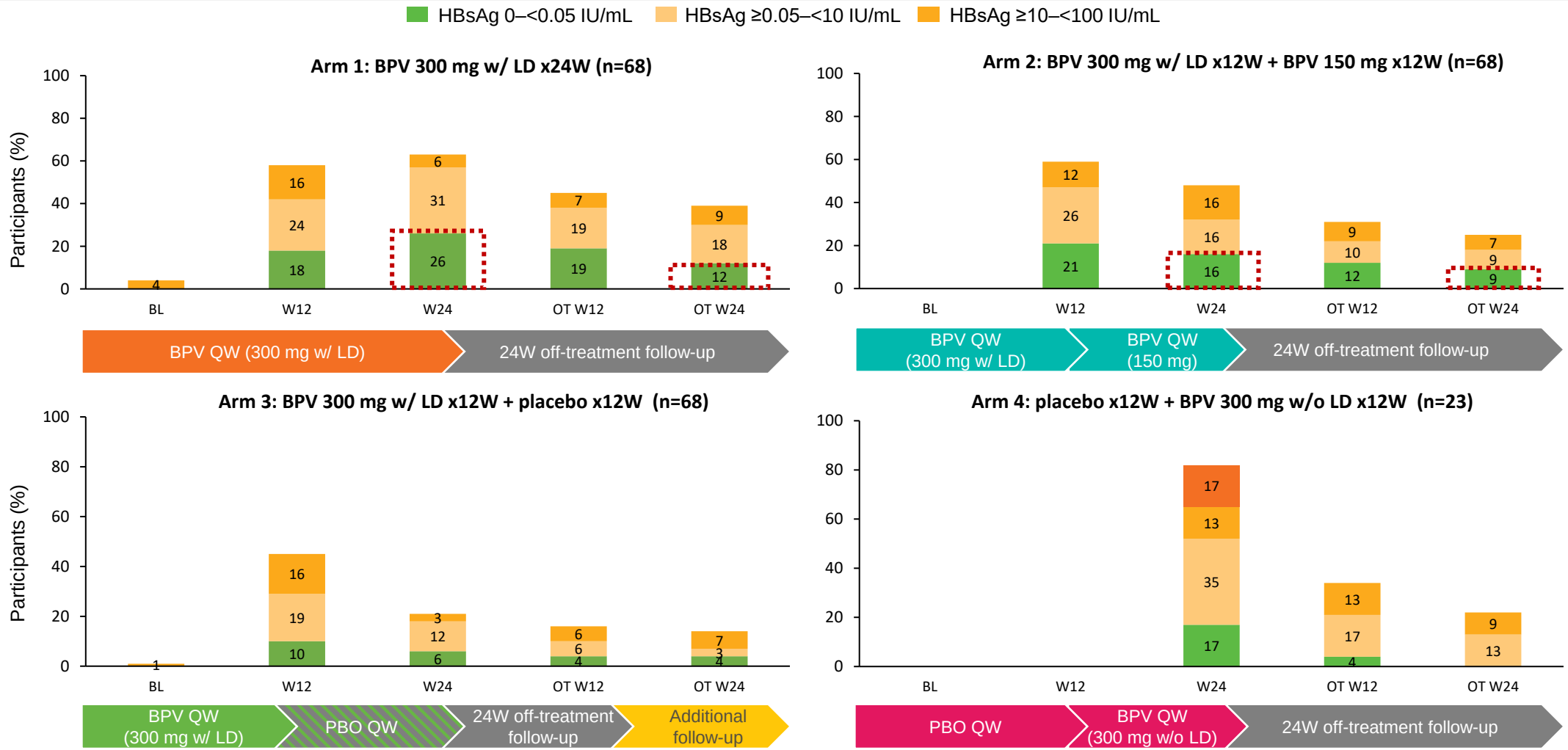
Primary endpoint (☆): Virologic response (HBsAg <LLOQ [0.05 IU/mL] and HBV DNA <LLOQ [20 IU/mL]) sustained for 24 weeks from planned end of bepirovirsen treatment in the absence of rescue medication

This analysis (▲): Participants achieving HBsAg <LLOQ and HBV DNA <LLOQ at end of bepirovirsen treatment

Yuen MF, et al. EASL 2022. #LB004A/4B. Sponsored by GlaxoSmithKline

B-Clear study – NUC suppressed
Approximately half of participants who achieved HBsAg loss after 24 weeks of treatment (Arms 1 and 2) maintained this loss at 24 weeks post end of treatment

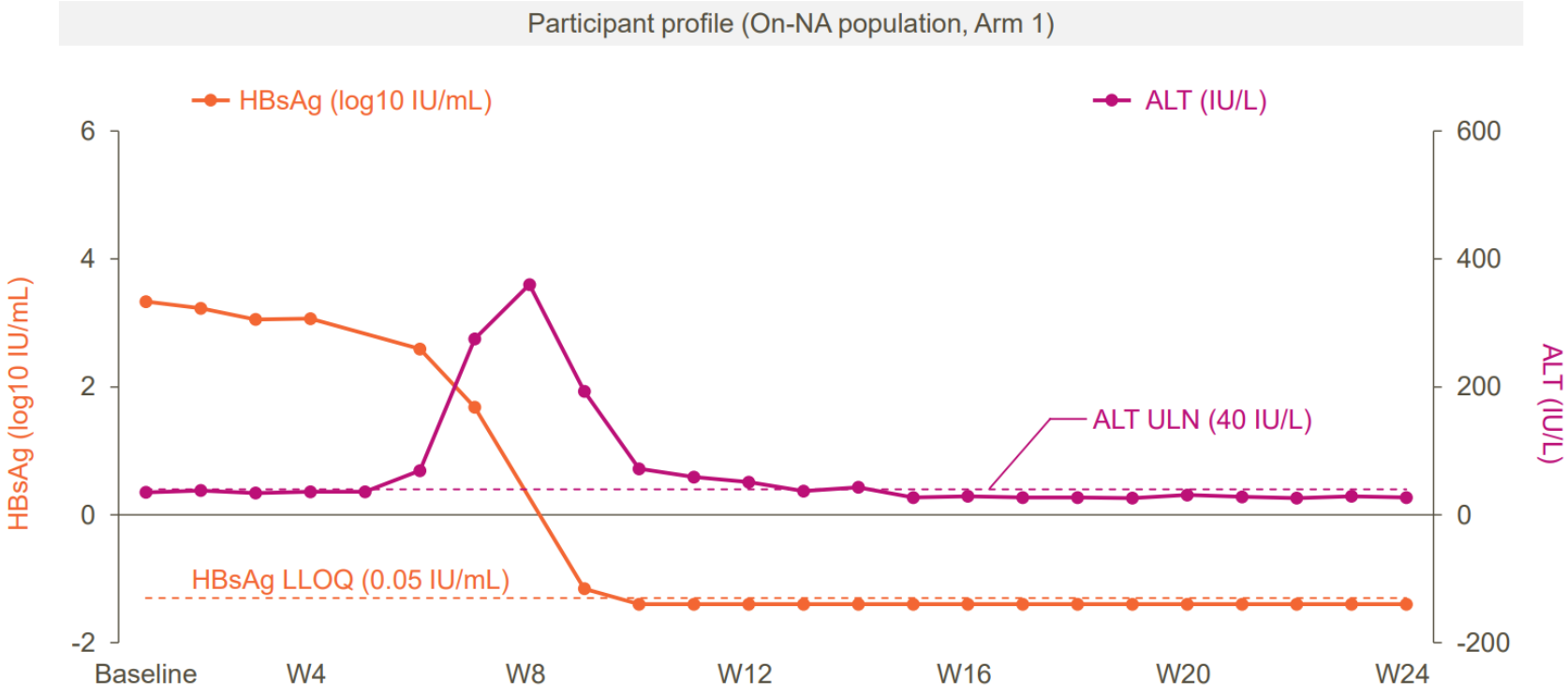
ITT population



Percentages calculated based on the total number of participants in the ITT population, therefore totals may not add up to 100% due to missing data.
BPV, bepirovirsen; BL, baseline; HBsAg, hepatitis B surface antigen; ITT, intent-to-treat; LD, loading dose; OT, off treatment; PBO, placebo; QW, once a week; W, week; w/=with; w/o=without.

Modified from Yuen MF, et al. AASLD 2022, LB oral

ALT elevation observed in association with most HBsAg declines



- Similar to data reported in the Phase 2a study,[1] the ALT increase occurred concomitantly with HBsAg reduction.

B-Clear study
Safety among patients with CHB treated with bepirovirsen ± NUCs

Safety	Patients receiving NUCs				Patients not receiving NUCs			
n (%)	300 mg w/LD x24wk	300 mg w/LD x12wk +150 mg x12wk	300 mg w/LD x12wk +PBO x12wk	PBO x12wk +300 mg w/o LD x12wk	300 mg w/LD x24wk	300 mg w/LD x12wk +150 mg x12wk	300 mg w/LD x12wk +PBO x12wk	PBO x12wk +300 mg w/o LD x12wk
n	68	67	68	23	70	67	68	24
Any AE	**54 (79)**	**58 (87)**	**53 (78)**	**16 (70)**	**64 (91)**	**58 (87)**	**61 (90)**	**18 (75)**
Study related	47 (69)	53 (79)	51 (75)	15 (65)	64 (91)	53 (79)	57 (84)	17 (71)
Treatment discontinued	2 (3)	3 (4)	3 (4)	0	3 (4)	1 (1)	5 (7)	0
Grade 3 or 4 AEs	7 (10)	9 (13)	8 (12)	0	16 (23)	14 (21)	12 (18)	4 (17)
Any SAEs	**1 (1)**	**1 (1)**	**4 (6)**	**0**	**6 (9)**	**2 (3)**	**2 (3)**	**0**
Study-related	1 (1)[a]	0	0	0	3 (4)[b]	0	0	0
Fatal	0	0	0	0	0	0	0	0

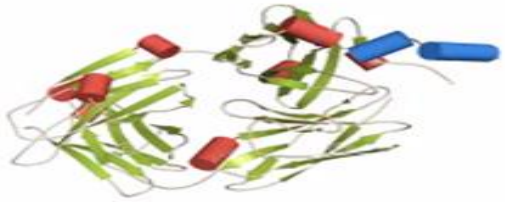
[a]**Study-related AE**: cryoglobulinemia

[b]**Study-related AEs:** SIRS; HBV; liver dysfunction

Phase III registration study planned in 2023

Yuen MF, et al. EASL 2022. #LB004A/4B.

Targets for Combination of New Therapies

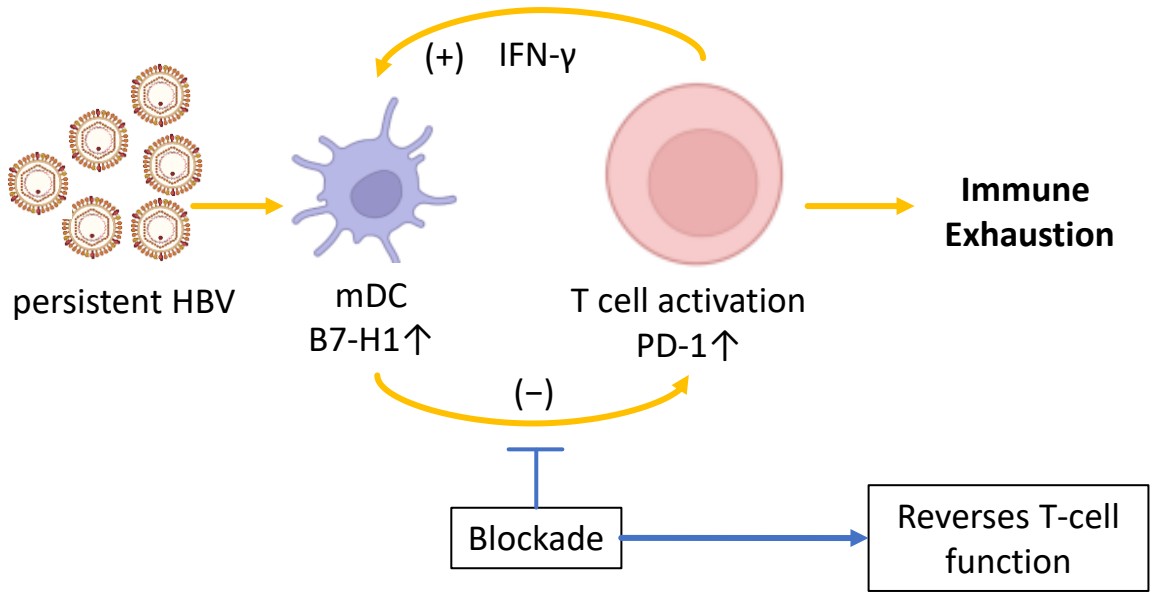


Replication inhibition	Antigen reduction	Immune stimulation	
Capsid Assembly Modulators (CAMs)	Small interference RNA (sIRNA)	Revive Immune-response TLR-8 agonist TLR-7 agonist Check Point inhibitors Anti-PDL Anti-PDL1	B/ T cell response Therapeutic Vaccines
Nucleos(t)ide Analogues	Antisense Oligonucleotide (ASO)		
	Nucleic Acid Polymers (NAPs) S-antigen transport – inhibiting oligonucleotide polymers (STOPs)		

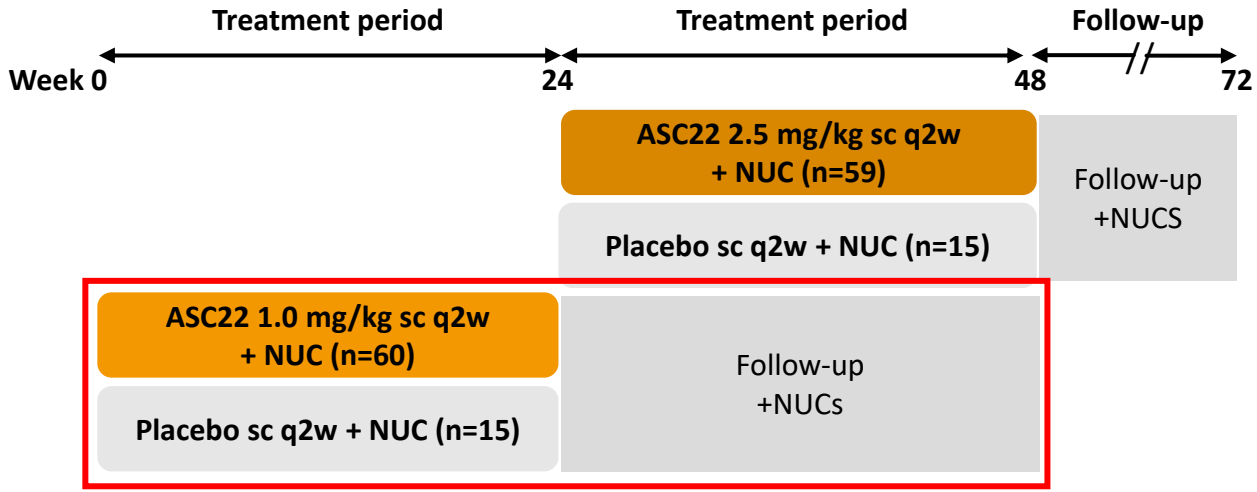
Phase 2b study in CHB patients with 24 weeks of PD-L1 Ab ASC22 (envafolimab) plus NUCs (interim results)

Phase 2b, randomized, single-blind, multicenter trial assessing the efficacy and safety of ASC22, a subcutaneous PD-L1 antibody, plus NUCs in patients with CHB

PD-L1 and chronic hepatitis B



Study design



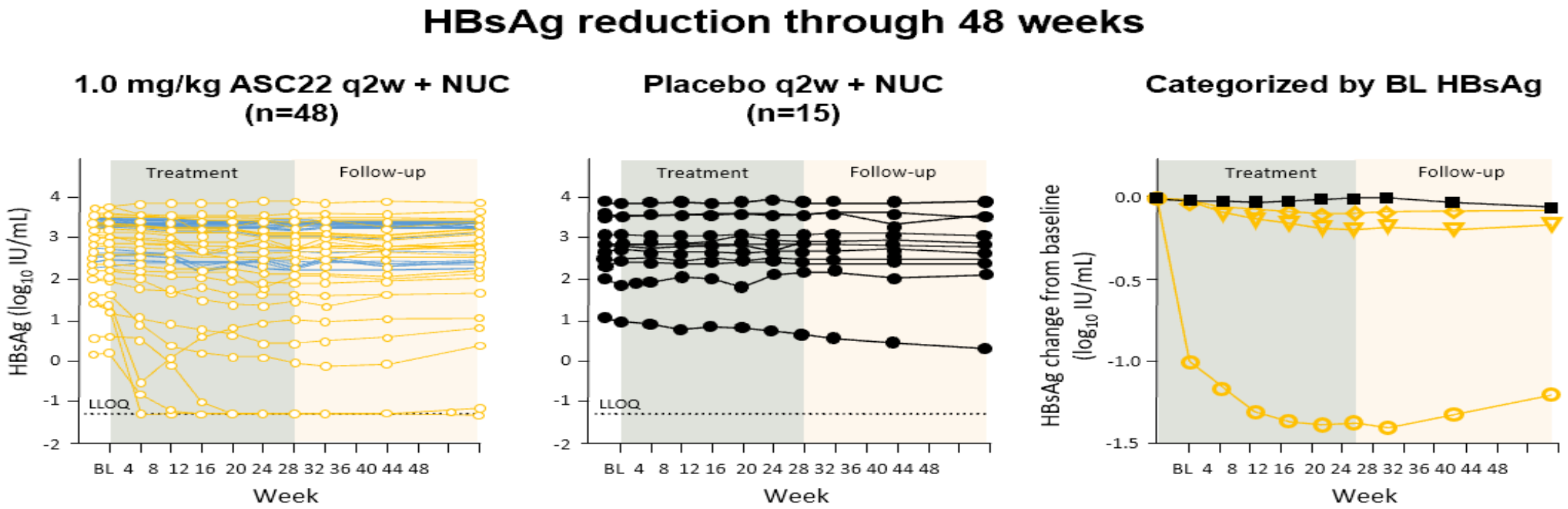
Safety population: 60+15
FAS: 48+15
10 dropouts

Inclusion criteria

- HBsAg ≤10,000 IU/mL
- HBV DNA <20 IU/mL
- ALT/AST <2x ULN
- HBeAg−

Wang G, et al. EASL 2022. #OS091.

Phase 2b: HBsAg reductions among patients with CHB treated with ASC22 (envafolimab) plus NUCs for 24 weeks

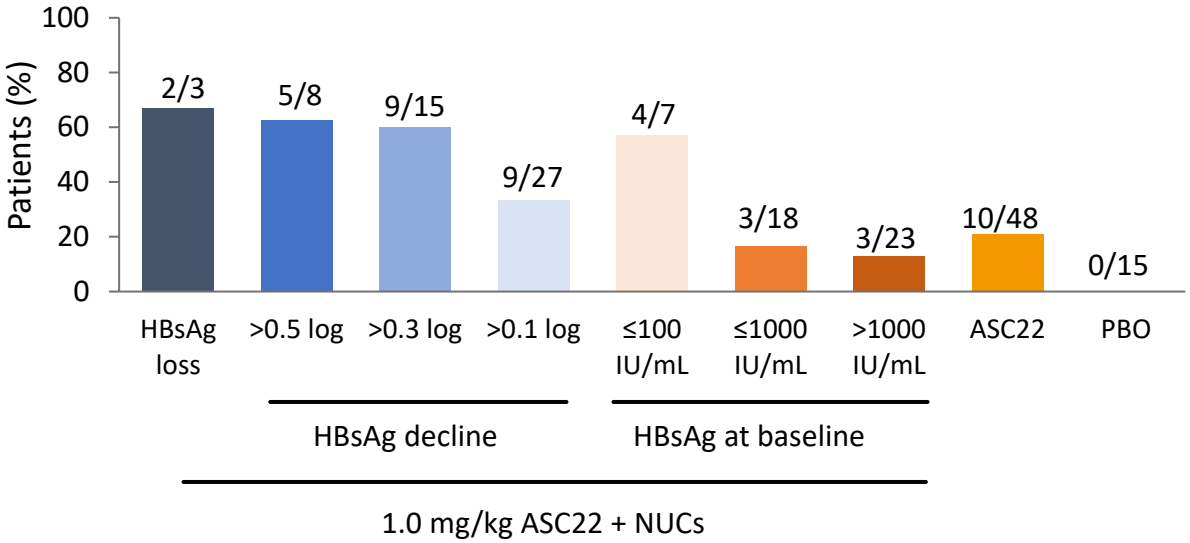


- 3 patients with baseline HBsAg ≤100 IU/mL (3/7, 42.9%) obtained sustained HBsAg loss (below LLOQ: 0.5 IU/mL)
- Patients with baseline HBsAg ≤100 IU/mL had more significant HBsAg reduction
- 2/3 patients with sustained HBsAg loss experienced ALT flares

Wang G, et al. EASL 2022. #OS091.

Phase 2b: On-treatment ALT flares and HBsAg reductions among patients with CHB treated with ASC22 (envafolimab) plus NUCs for 24 weeks

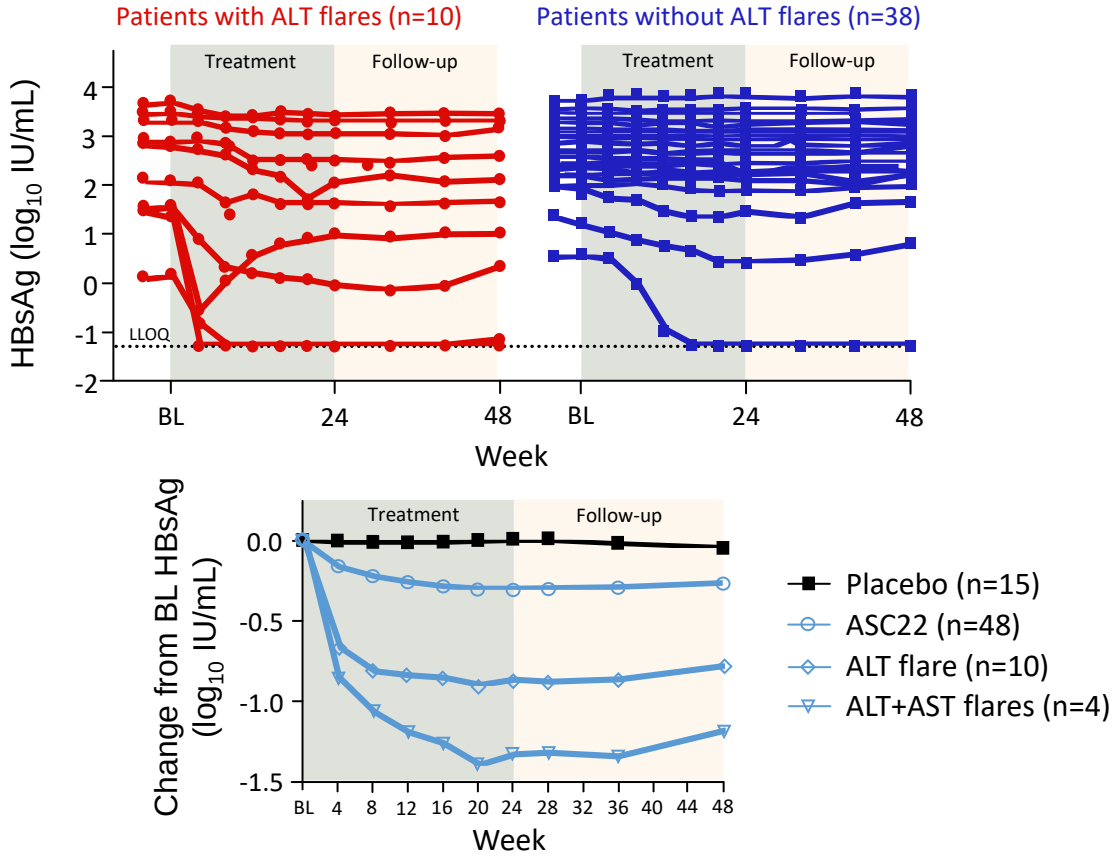
On-treatment ALT flares[a]



[a]An ALT and/or AST flare is defined as ALT or AST greater than 3-fold baseline level and more than 2xULN

- ALT flares were observed in 10/48 (21%) patients in the ASC22 group compared to none in the PBO group
- ALT flares were more frequent in patients with more HBsAg reduction or with lower baseline HBsAg

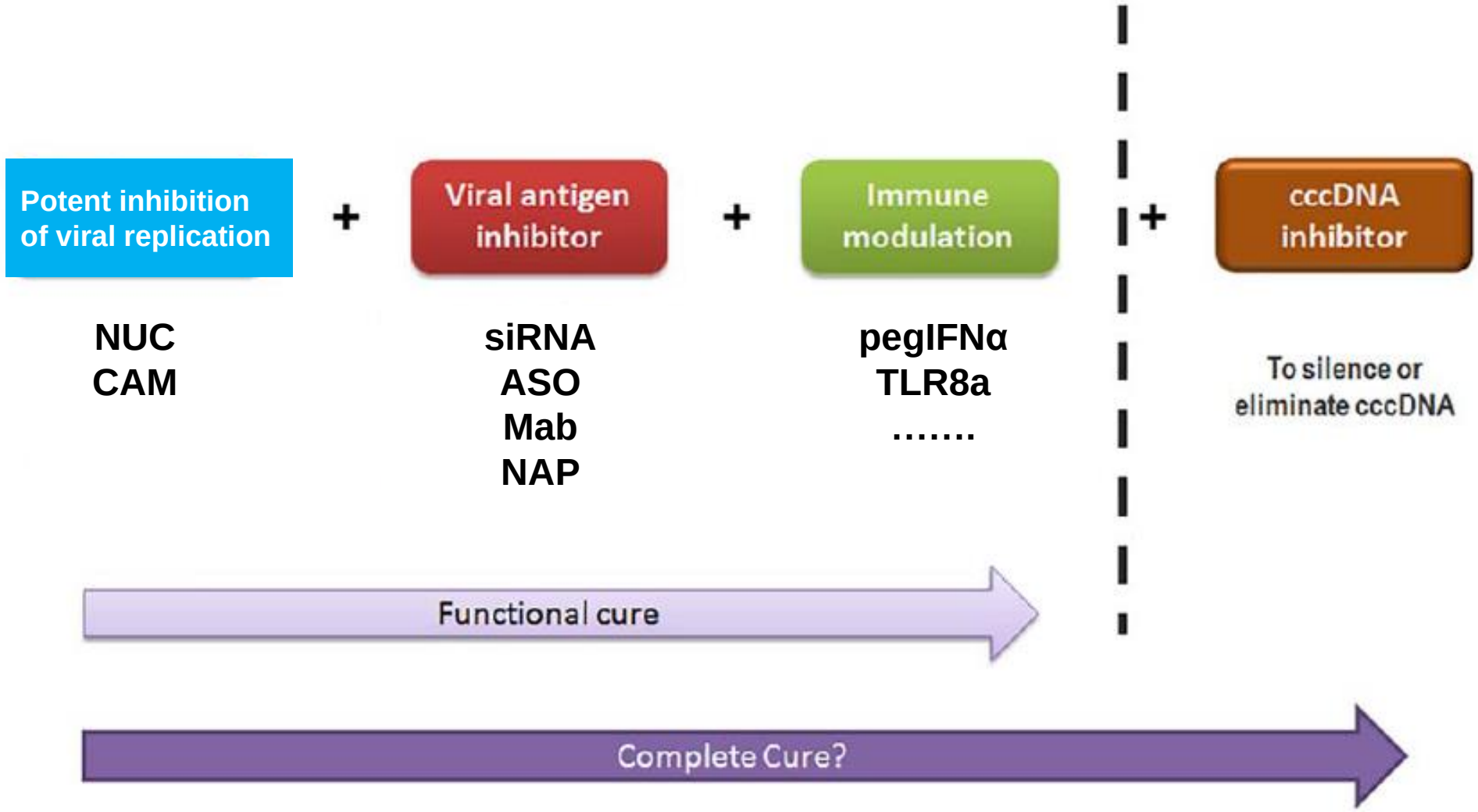
Change in HBsAg in patients with or without ALT flares



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

Wang G, et al. EASL 2022. #OS091.

The possible future curative regimen for hepatitis B



modified from Seto WK And Yuen MF. Clinical Liver Disease 2016;8,4, 83-88

CHRONIC HEPATITIS D

48-week integrated efficacy of bulevirtide monotherapy in Phase 2 and 3 trials for CHD

MYR202, Phase 2b (N=120, completed)

MYR203, Phase 2b (N=90, completed)

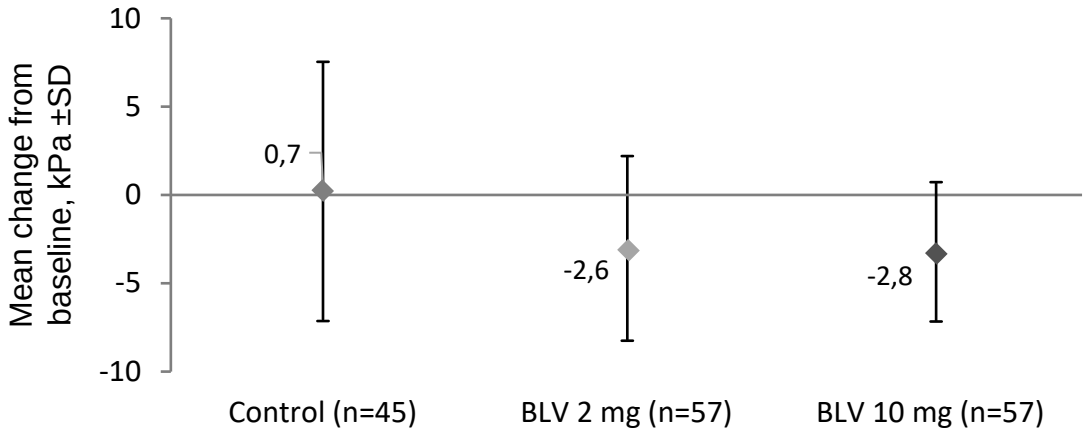
MYR204, Phase 2b (N=175, ongoing)

MYR301, Phase 3 (N=150, ongoing)

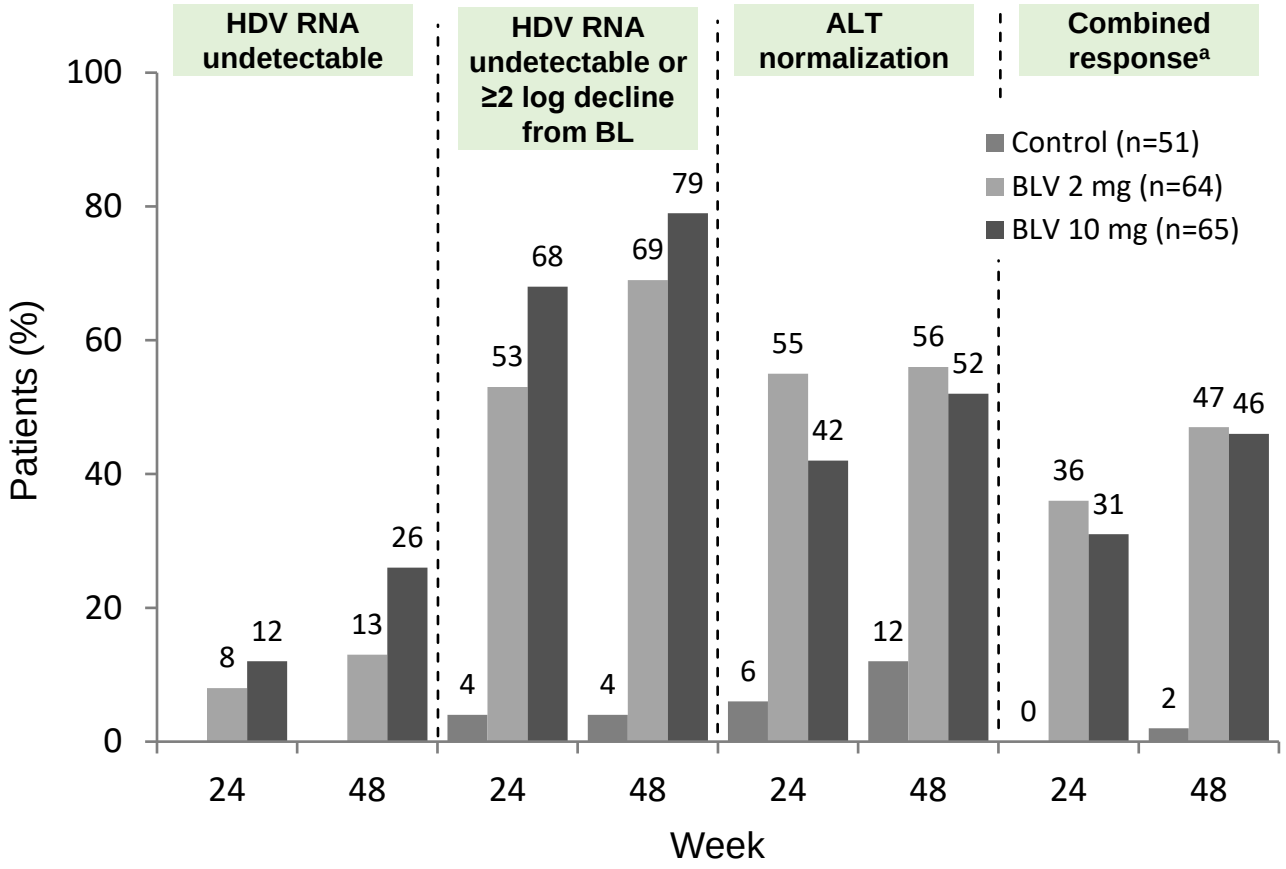
Week 48 integrated efficacy analysis (N=180)

- Control group[a] (n=51)
- BLV 2 mg (n=64)
- BLV 10 mg (n=65)

Change from baseline in liver stiffness at Week 48



Virological and biochemical responses through Week 48



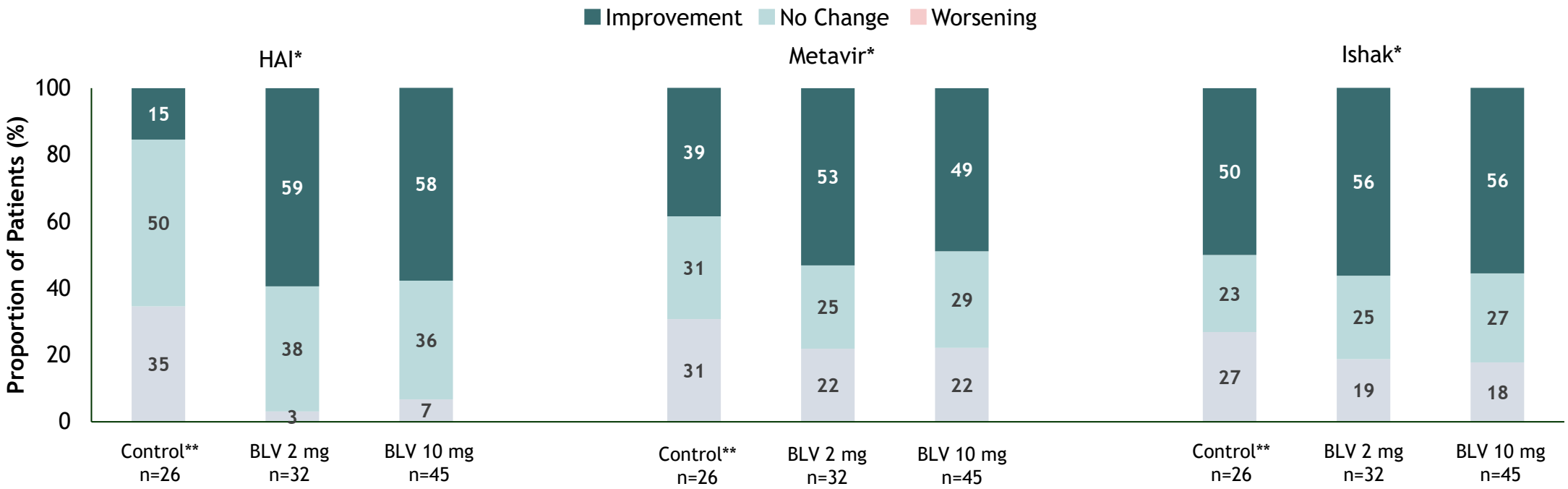
[a]Undetectable HDV RNA or 2 log decline from baseline and ALT normalization

Lampertico P, et al. AASLD 2022. Poster #1024. Sponsored by Gilead Sciences, Inc.

Hepatic Inflammation and Fibrosis at Week 48 of BLV

Histological sub-analysis in 103 patients from MYR203 and MYR301 with paired liver biopsy at BL and Week 48

Hepatic Inflammation and Fibrosis Changes at Week 48

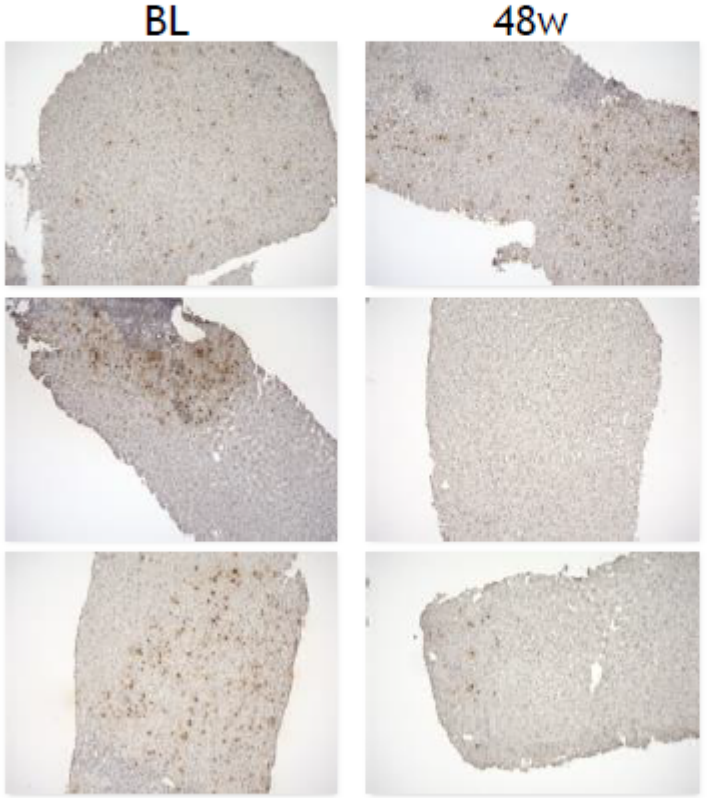


Most participants treated with BLV had stable or improved hepatic inflammation and fibrosis responses at Week 48

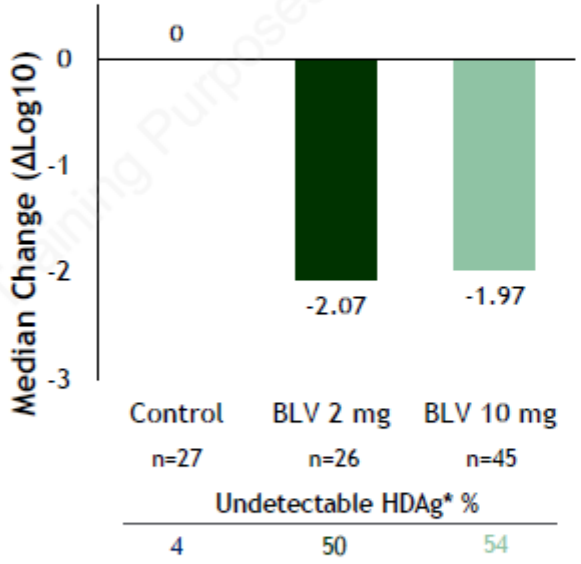
*Change at Week 48; **No treatment through Week 48. BLV bulevirtide; HAI, histologic activity index.
Lampertico P, et al. DeltaCure 2022. Poster #39

Integrated Paired Biopsy Analysis at 48 Weeks

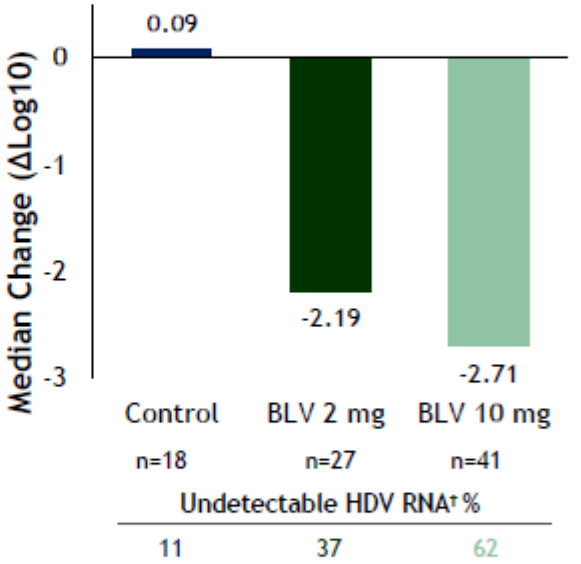
Intrahepatic analysis of HDV biomarkers at 48 weeks of BLV treatment



HDAg-Positive Hepatocytes



Intrahepatic HDV RNA Levels



48 weeks of BLV led to a marked drop in HDV-infected hepatocytes

*Lower limit of detection = 0.01% of positive cells; †Lower limit of detection not provided
BLV, bulevirtide; BL, baseline; HDAg, hepatitis delta antigen.
Allweiss L, et al. International HBV Meeting 2022. Presentation #49

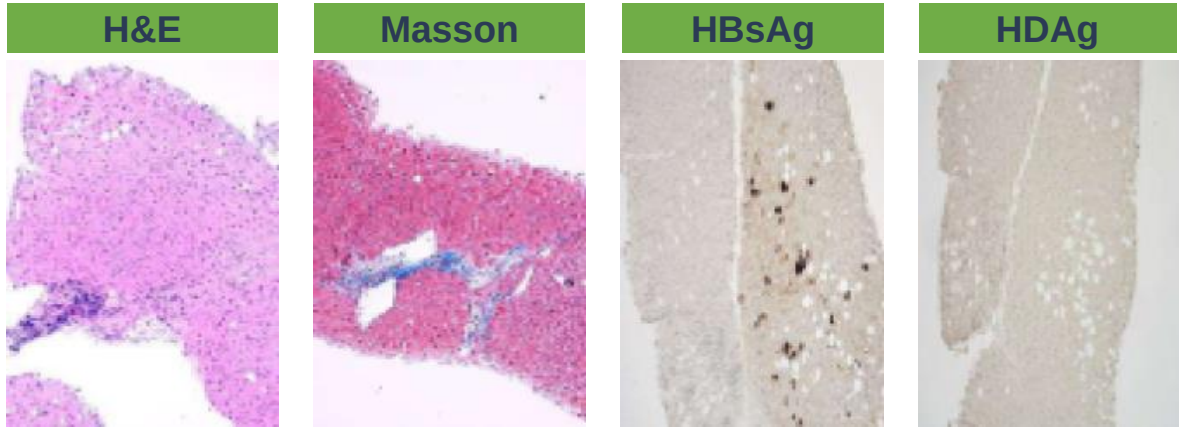
Curative effect of 3 years' bulevirtide monotherapy in a patient with compensated advanced cirrhosis

- 54-year-old Caucasian male with HDV-related compensated cirrhosis
- 3 years' bulevirtide monotherapy followed by 48 weeks' post-treatment monitoring
- TDF was continued also in the off-BLV period

			Off-BLV therapy weeks			
	BL	EOT BLV (Wk 144)	12	24	36	48
ALT/AST, U/L	232/179	28/36	23/30	44/50	31/36	30/33
ALP/gGT, U/L	185/231	82/110	82/77	88/226	110/72	56/68
pCHE, U/L	4479	7805	7200	8440	8313	8923
Albumin/ γglobulin, g/dL	3.6/2.9	4.6/1.0	4.5/1.0	4.5/1.1	4.3/1.0	4.6/1.1
IgG, mg/dL	3077	1285	1240	1160	1185	1221
Platelets x10^9/L	74	110	137	115	144	144
LSM, kPa	17.6	10.9	8.5	11.5	-	10.6
HBsAg, IU/mL	9091	5045	2873	3238	2347	2316
HBcrAg, log U/mL	4.5	3.5	3.5	3.4	3.4	3.4
HBV RNA, cp/mL	<160	<10	<10	<10	-	<10
HDV RNA, IU/mL	392,000	<6	<6	<6	<6	<6
Bile acids, µmol/L	35	55	8	15	-	11

- 48-week off-therapy liver biopsy showed minimal features of inflammation – significant improvement of liver fibrosis (Ishak Grading 1 Staging 4) and resolution of autoimmunity features

48-weeks post-BLV therapy liver biopsy



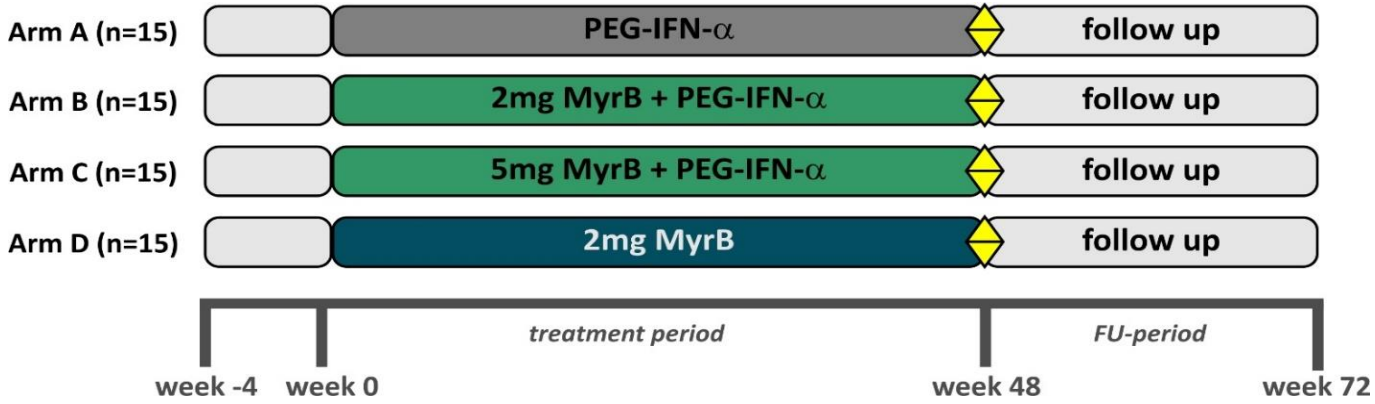
HBsAg stained positive in 0.4% of biopsy – HBcAg and cccDNA negative
HDAg stained negative and HDV RNA undetectable

- Unique case: HDV cure (serum and liver) 48 weeks after BLV discontinuation in a patient with compensated cirrhosis and esophageal varices despite HBsAg remaining positive
- How can you cure HDV with an entry inhibitor if HBsAg remains positive? Doesn't occur often, but does appear possible
- Any role for long-term TDF therapy?
- Excellent clinical response

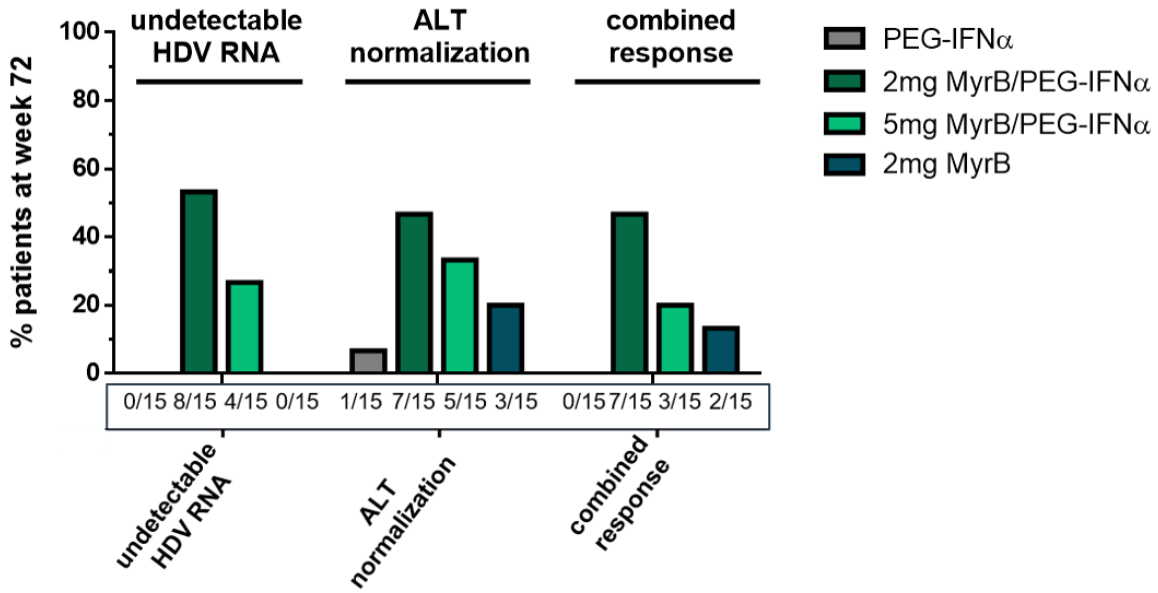
Safety and efficacy of Bulevirtid+ PEG-interferon α 2a for 48 wks in CHD patients :a phase 2 trial (MYR203)

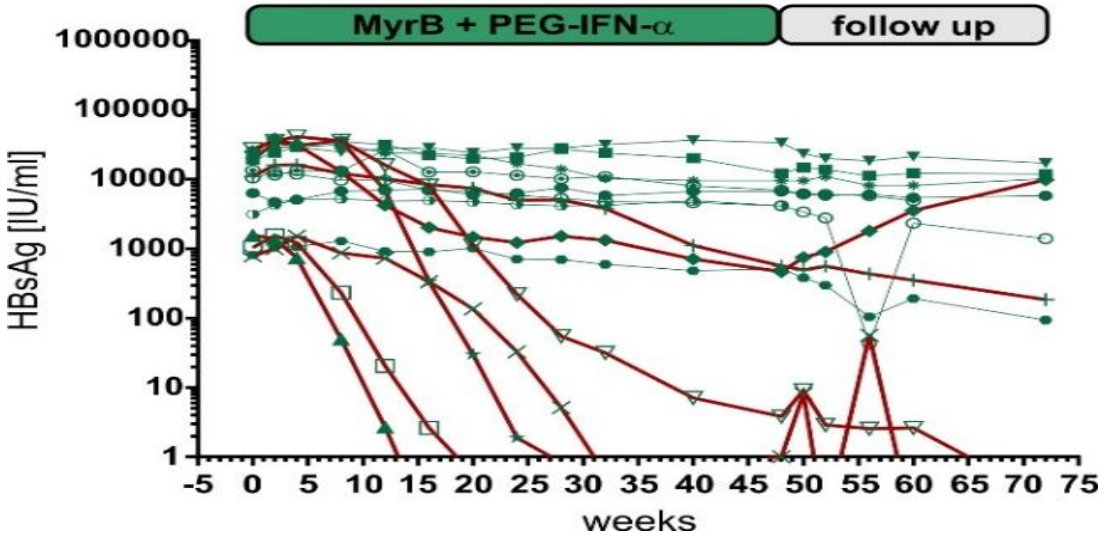
60 patients CHD randomized

Primary endpoint: HDV RNA undetectable at Week 24 of follow up



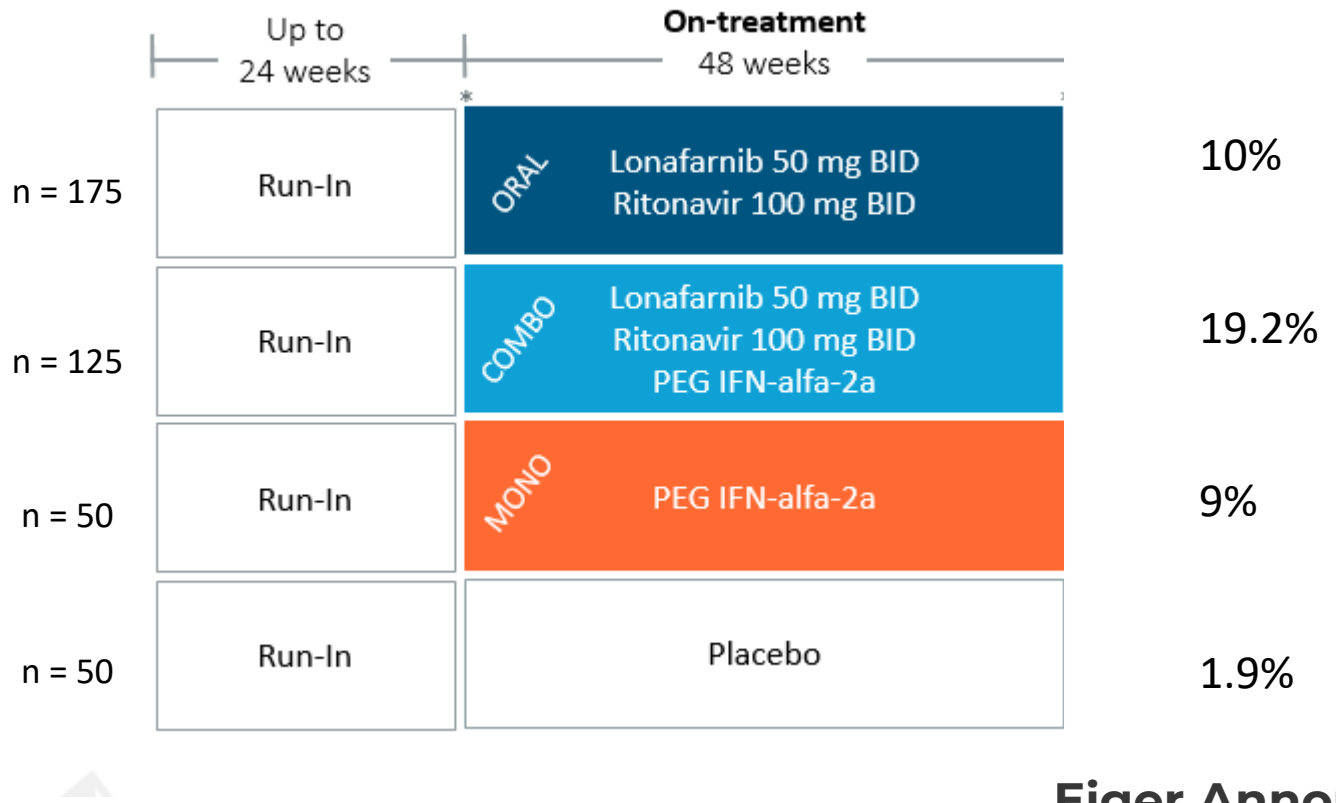
2 mg MyrB plus PEG-IFNα achieved HDV RNA undetectable and HBsAg loss in 40%





Wedemeyer H, et al. ILC 2019; GS-13

Lonafarnib phase 3 Global Study in CHD: D-LIVR



Primary Endpoint at Week 48

≥ 2 log decline in HDV RNA

+

Normalization of ALT

Secondary Endpoint at Week 48

Histologic improvement

Improvement of fibrosis

* biopsy;
All patients will be maintained on background HBV nucleoside therapy.
Superiority over PEG IFN-alfa-2a not required.

Eiger Announces Both Lonafarnib-based Treatments in Pivotal Phase 3 D-LIVR Trial in HDV Achieved Statistical Significance Against Placebo in Composite Primary Endpoint
December 2022

https://clinicaltrials.gov/ct2/show/NCT03719313
Keskin et al, *Clin Gastrol Hep* **2015**

Summary May 2023:

- Significant decline of HBsAg levels observed with many new therapies…..
- but HBsAg loss (~25-30%) only with 3 drugs:
  - ASO (GSK 836) at week 24 on-therapy
  - siRNA (VIR) + NUC + pegIFNα at week 48 on-therapy
  - ASC22 (envafolimab) plus NUCs for 24 weeks
- ....but 24-week off-therapy data limited: 11% HBsAg loss with ASO
- Some compounds have been discontinued due to non response or safety issues
- Hepatitis D viremia become undetectable 13% of cases after 48 of therapy but very few data off therapy