Capsid Assembly Modulators

Man-Fung Yuen

MBBS, MD, PhD, DSc

Chair Professor

Li Shu Fan Medical Foundation Professor in Medicine

Chief, Division of Gastroenterology and Hepatology, Queen Mary Hospital

Deputy Head, Department of Medicine, The University of Hong Kong

Hong Kong

HKU Med LKS Faculty of Medicine The University of Hong Kong 香港大學李嘉誠醫學院

Disclosure

- Advisor/ consultant:
  - AbbVie, Arbutus Biopharma, Assembly Biosciences, Bristol Myer Squibb, Clear B Therapeutics, Dicerna Pharmaceuticals, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, Roche, Springbank Pharmaceuticals, Roche

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  - Assembly Biosciences, Arrowhead Pharmaceuticals, Bristol Myer Squibb, Fujirebio Incorporation, Gilead Sciences, Merck Sharp and Dohme, Springbank Pharmaceuticals, Roche

- Speaker's bureau:
  - Arbutus Biopharma, Bristol Myer Squibb, Discerna Pharmaceuticals, Fujirebio Incorporation, Gilead Sciences, GlaxoSmithKline

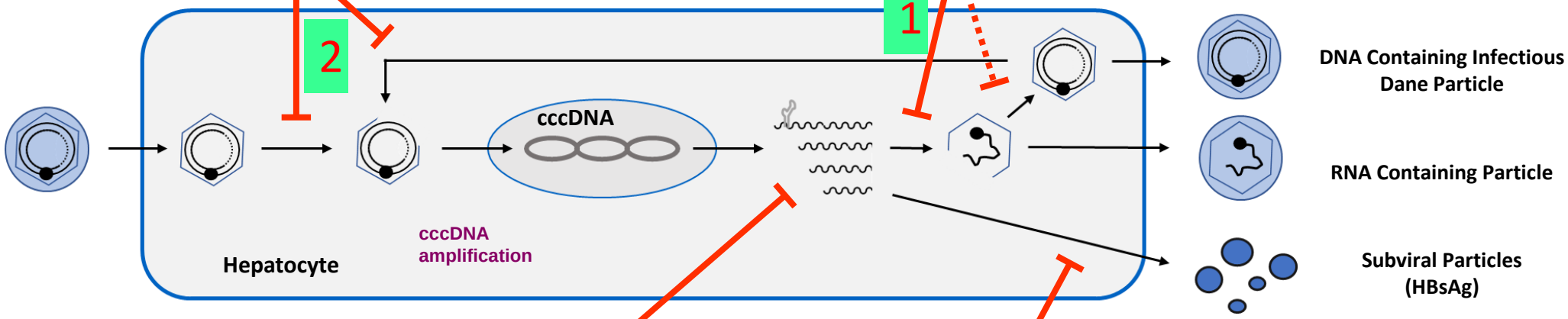
Modes of action of different novel direct antiviral agents

Block de novo formation and maintainance of cccDNA
Capsid Assembly Modulator (CAM)

Secondary MOA
Capsid disassembly & cccDNA formation

Primary MOA
pgRNA encapsidation & DNA replication

Inhibition of viral replication
CAM, Nucleoside Analogues (NA)

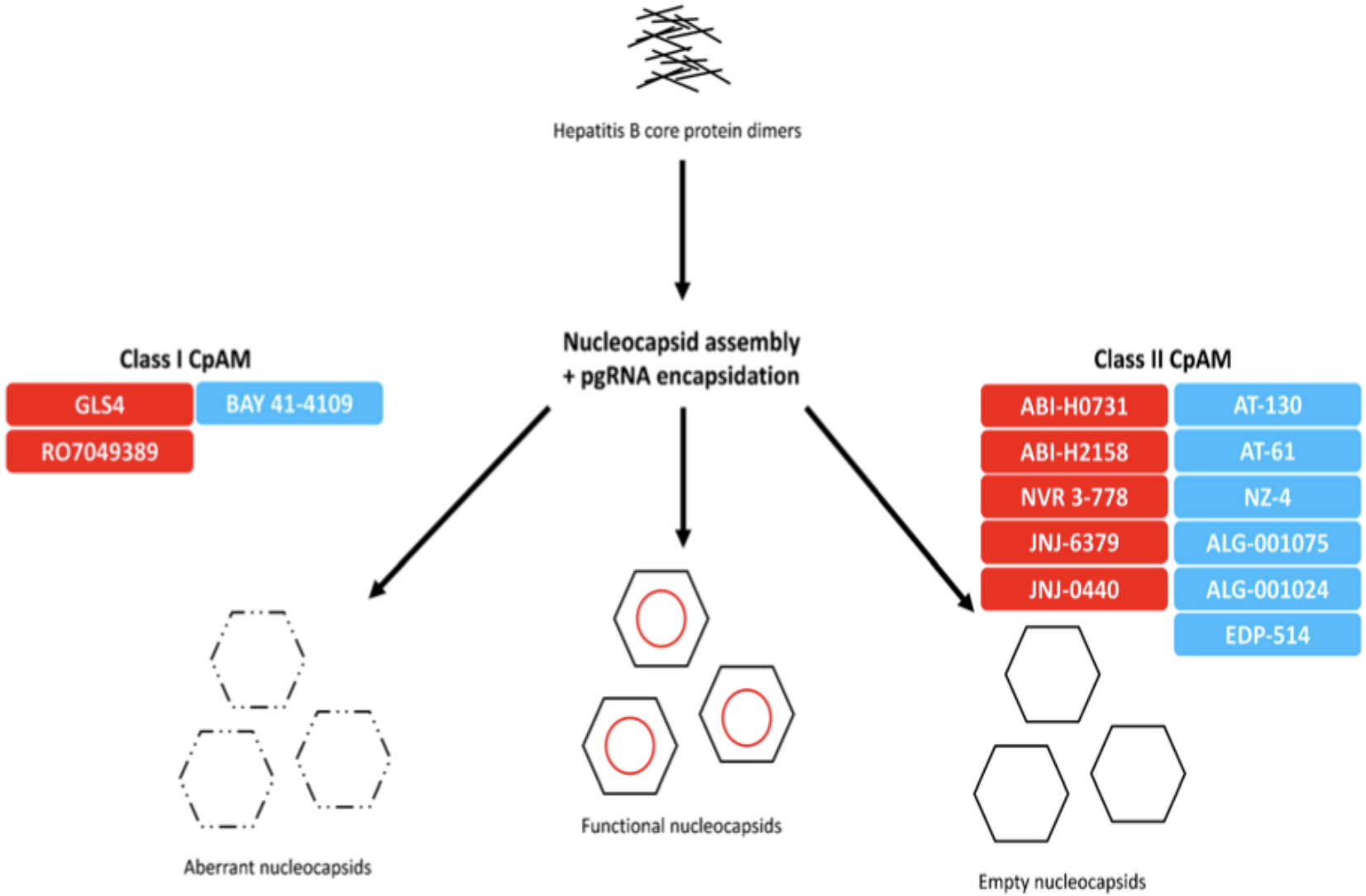


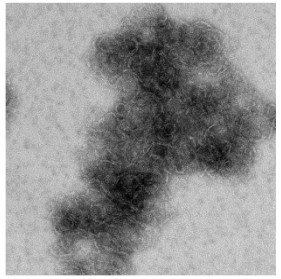
Inhibition of viral transcripts
HBV ASO, siRNA

Viral antigen load reduction
S-Antigen Transport-inhibiting Oligonucleotide Polymer

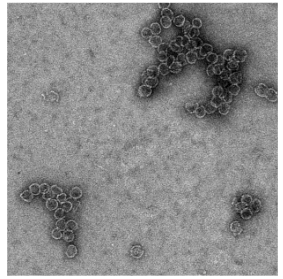
Adapted from L. Blatt, HepDart, 2017

Two types of CAM





Forms aberrant non-capsid polymers

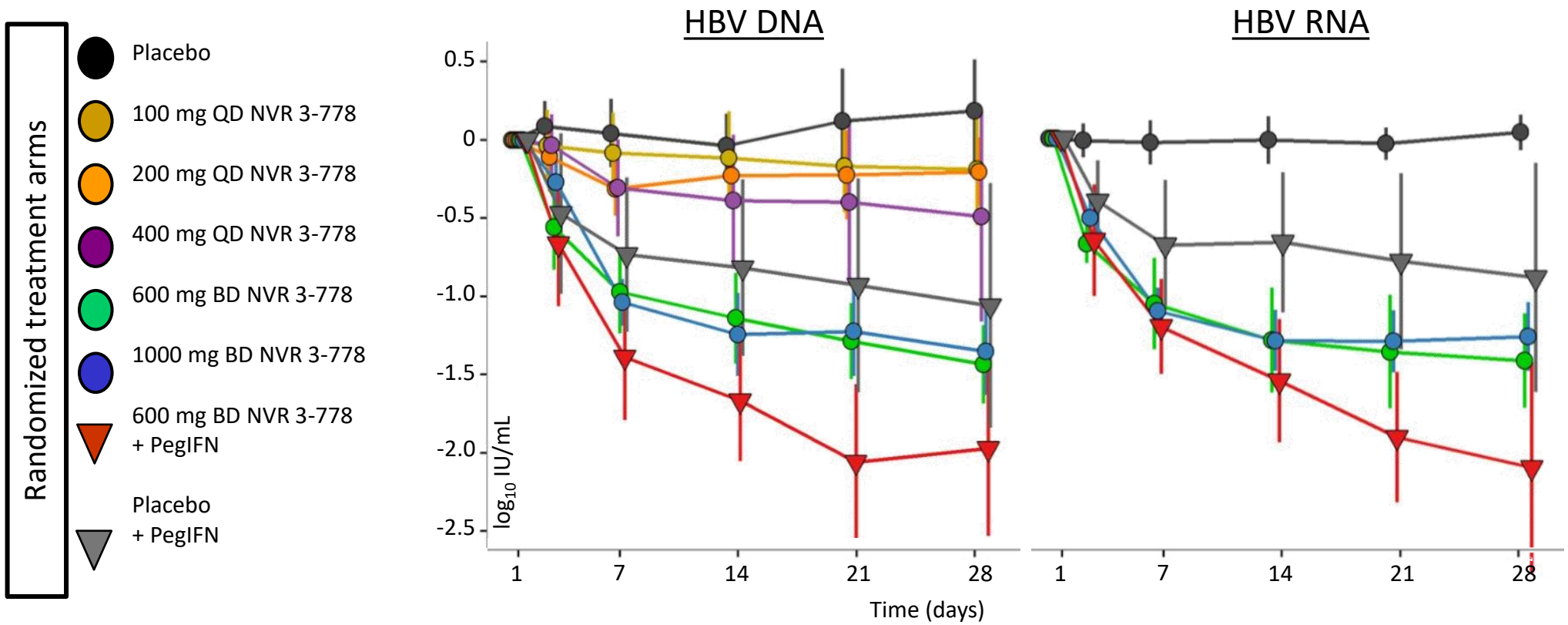


Forms empty capsid devoid of pgRNA/rcDNA

Hui R… Yuen MF. Curr Hepatol Reports 2020;19:293-301

Phase 1 studies: Short term 2-4 week treatment of CAM

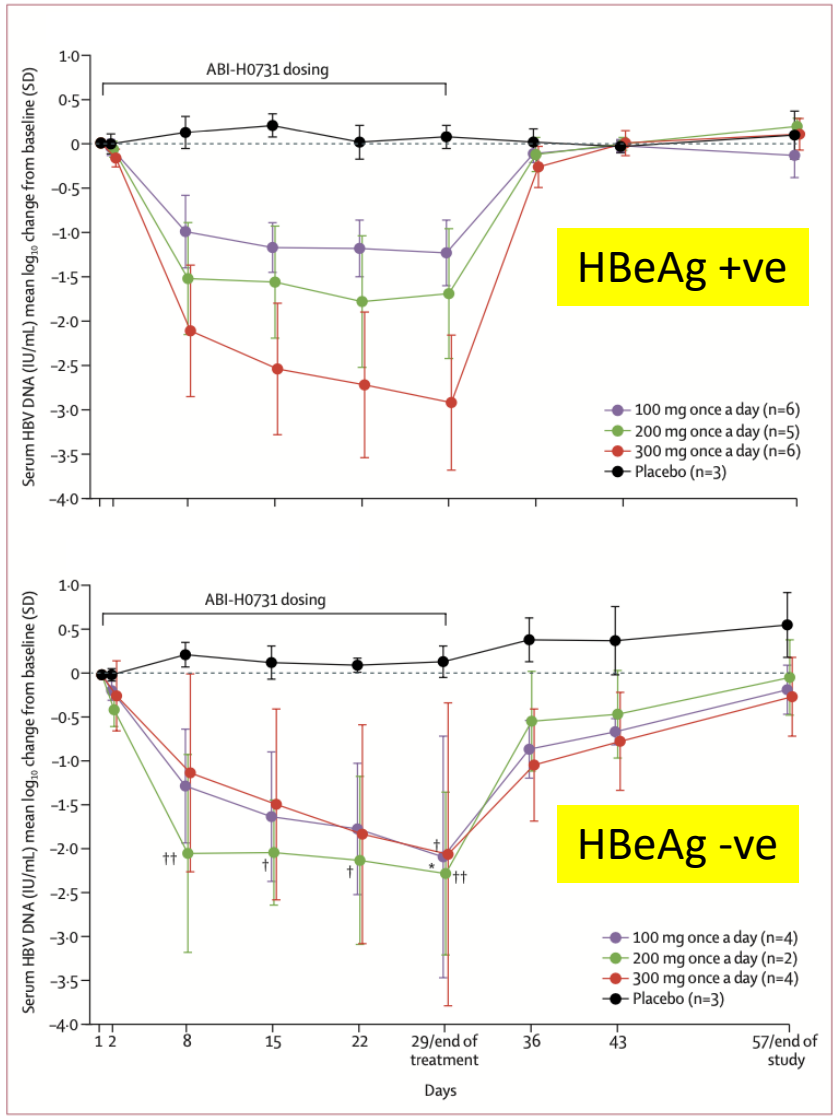
First-in-class CAM (NVR3-778) +/- Peg IFN



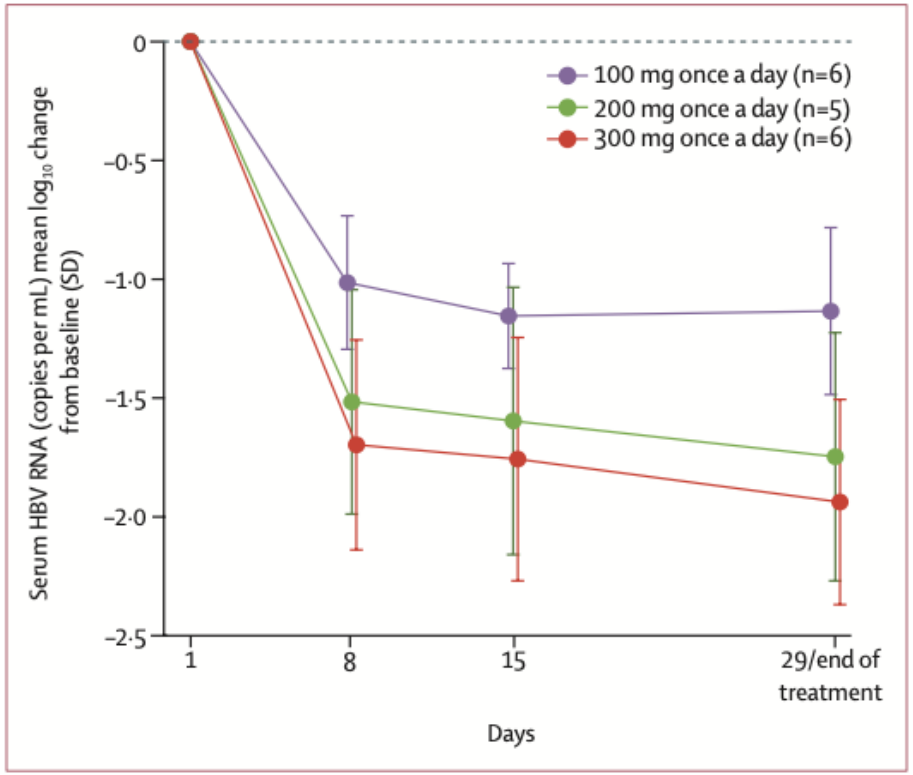
Yuen MF, et al. Gastroenterology 2019;156:1392-403

ABI-H0731 (Vebicorvir)

HBV DNA

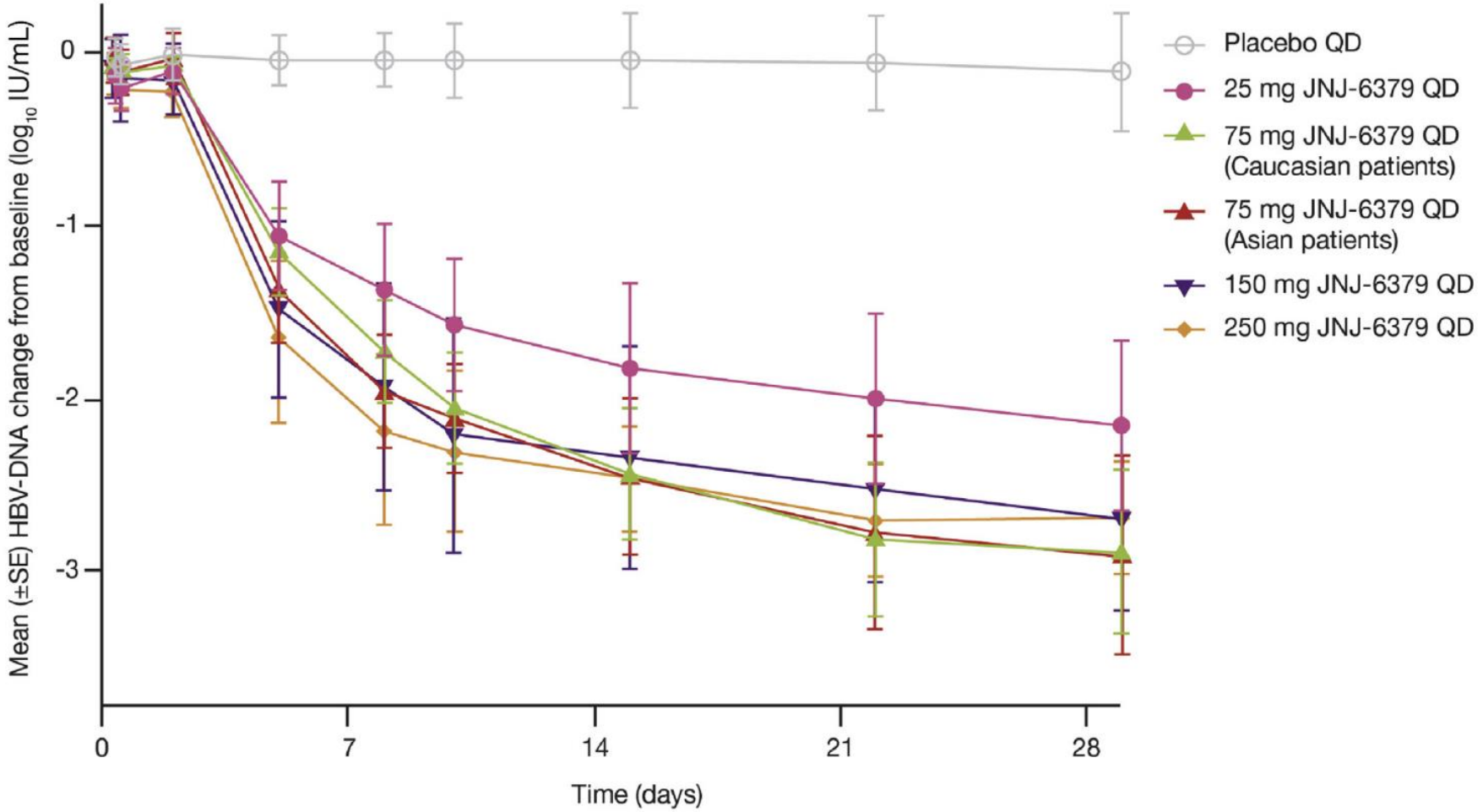


HBV RNA



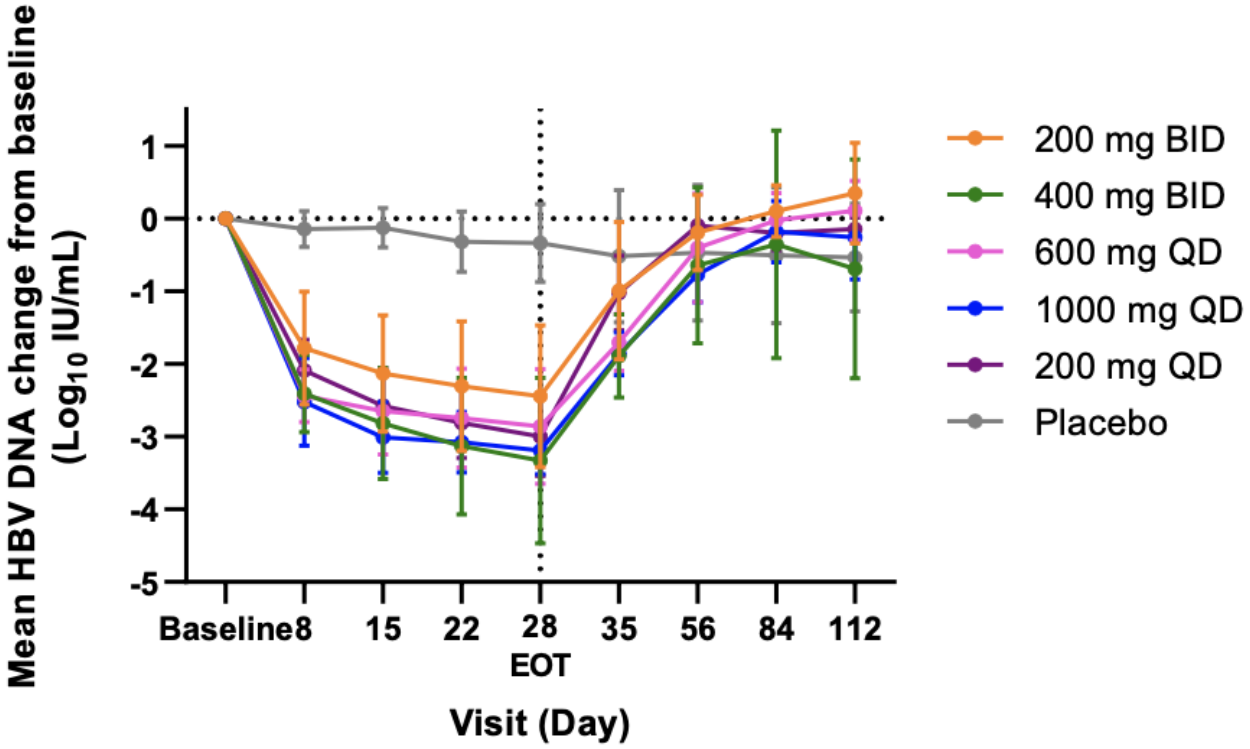
Yuen MF, et al. Lancet Gastroenterol Hepatol 2020:5:152-66

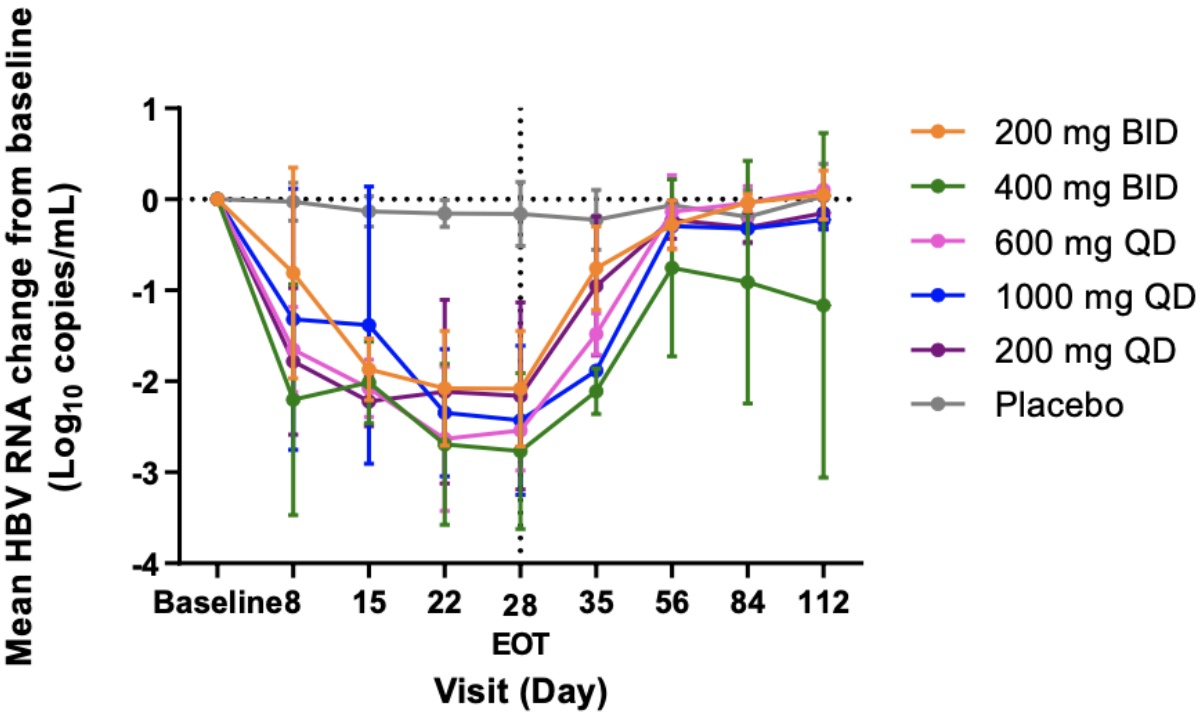
JNJ-5616379



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

RO7049389

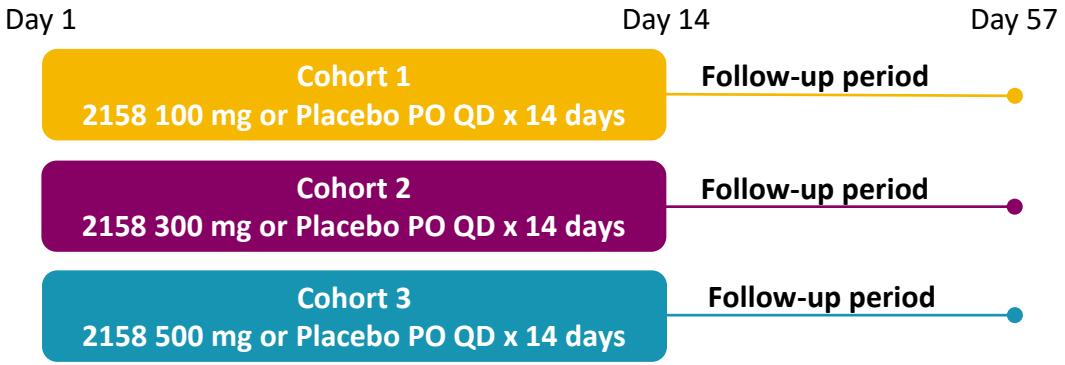




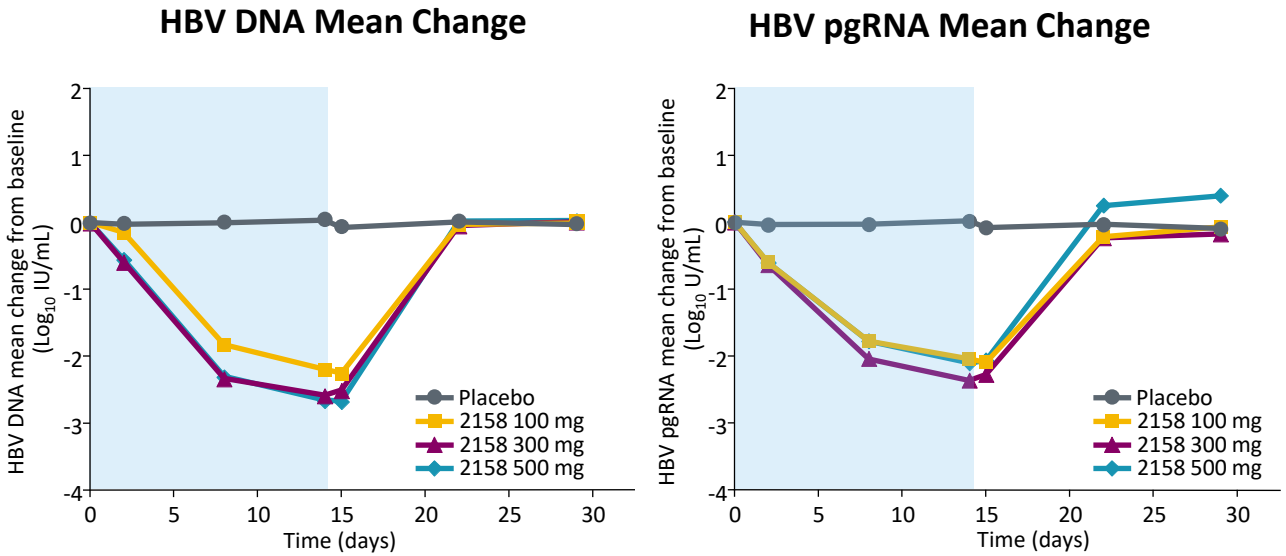
13/16 (81.3%) patients who were HBeAg negative at baseline achieved HBV DNA levels lower than LLOQ (<20 IU/mL).

Yuen MF, et al. Lancet Gastroenterol Hepatol (in press)

ABI-H2158 in HBeAg +ve patients: 2 weeks



Antiviral Efficacy

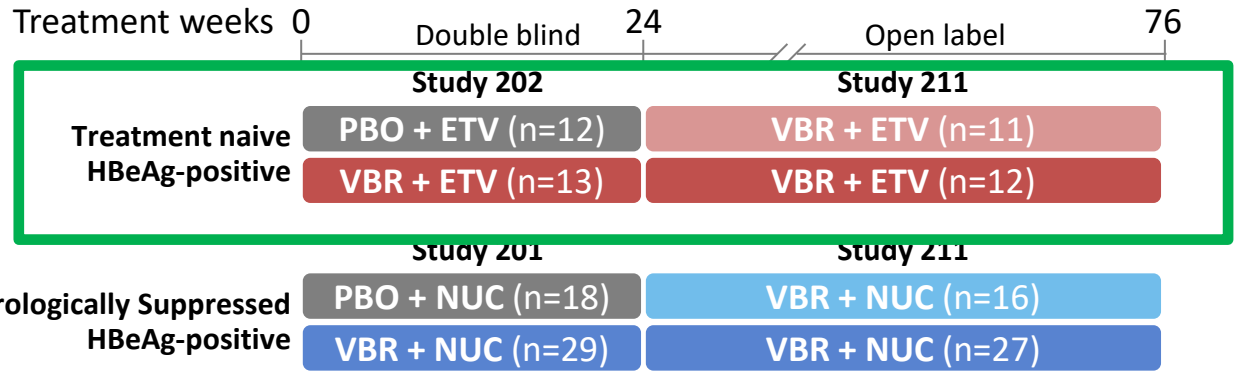


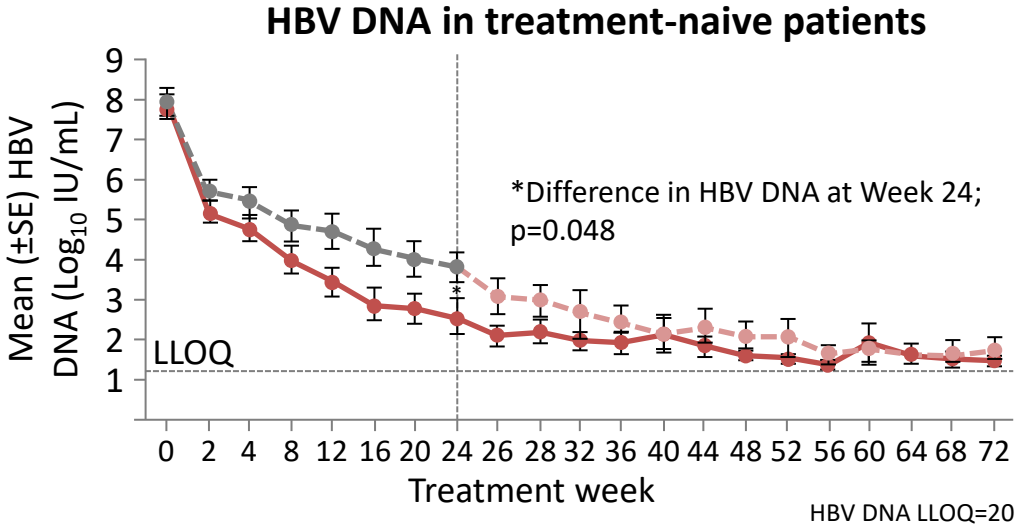
Mean change from baseline to Day 15	Placebo (n=6)	ABI-H2158 100 mg (n=7)	ABI-H2158 300 mg (n=7)	ABI-H2158 500 mg (n=7)
HBV DNA (range), Log_{10} IU/mL	−0.08 (−0.3 to 0.1)	−2.3 (−1.7 to −3.0)	−2.5 (−0.8 to −3.3)	−2.7 (−1.7 to −3.2)
HBV pgRNA (range), Log_{10} U/mL	−0.08 (−0.2 to 0.1)	−2.1 (−1.5 to −2.7)	−2.3 (−1.4 to −3.2)	−2.1 (−1.3 to −3.5)

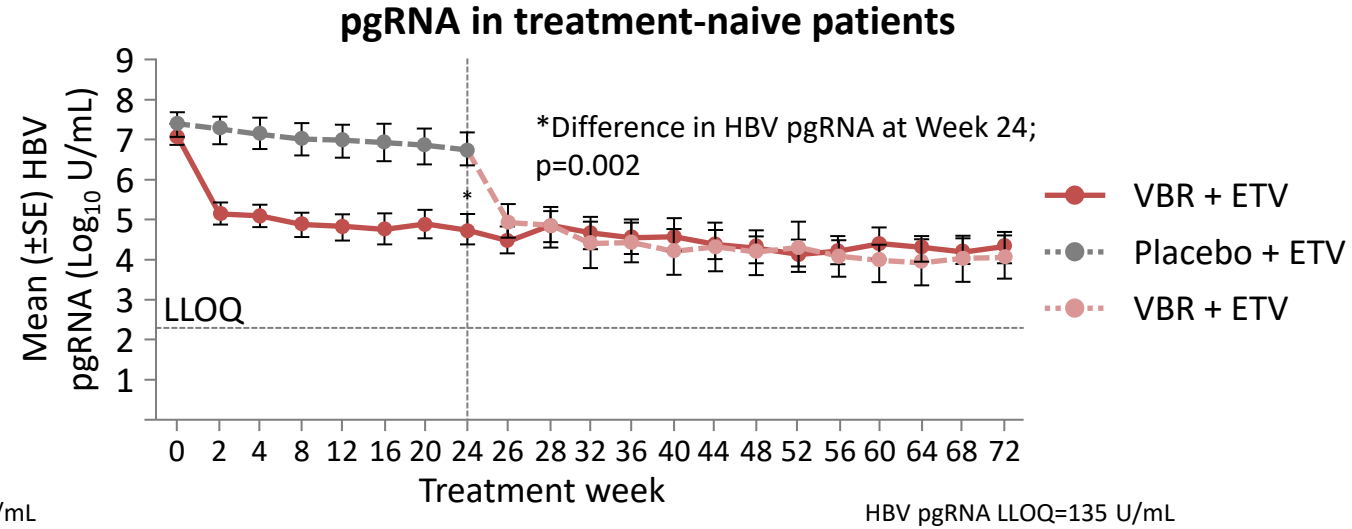
Agarwal K, et al. EASL dILC2020. #LBP5

Phase 2 studies: ≥ 24 week treatment of CAM

ABI-H0731 (vebicorvir) with NA
HBeAg +ve treatment naïve patients



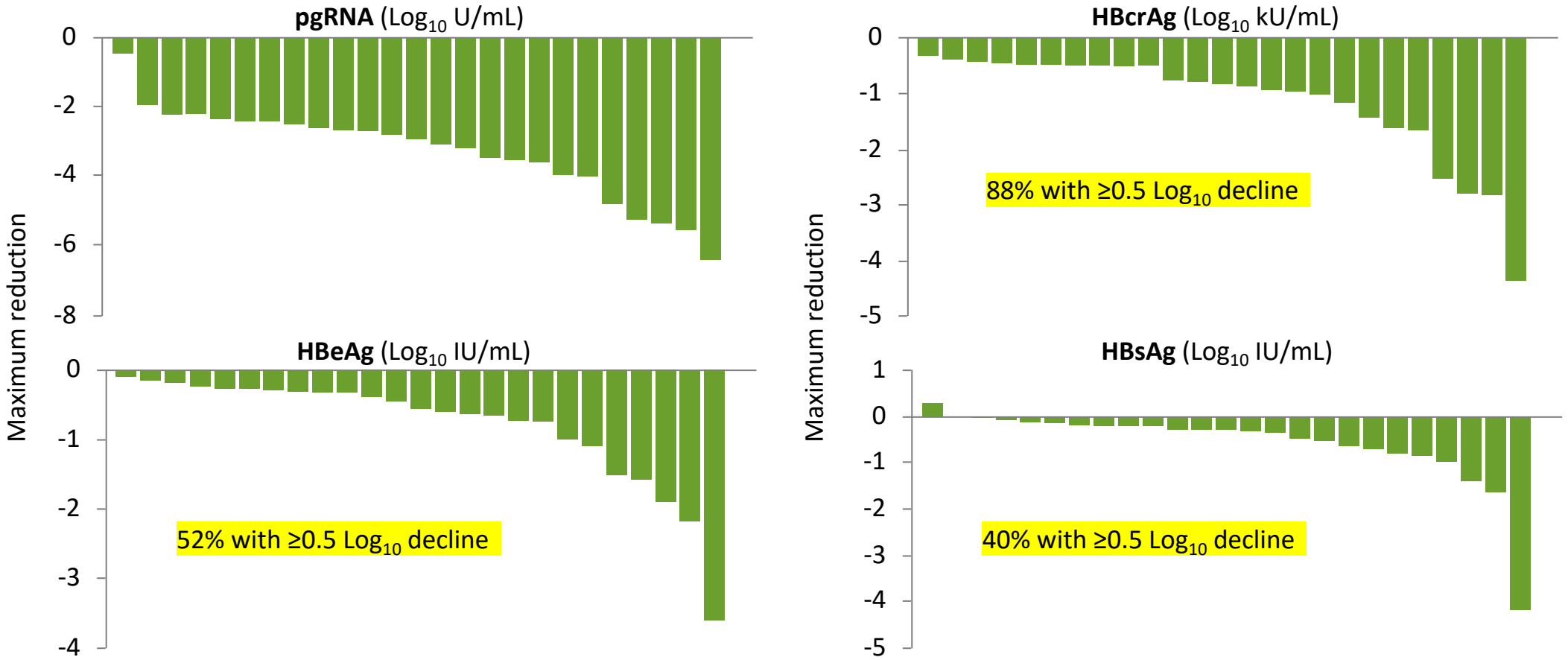




Yuen MF, et al. EASL dILC2020. #LBP30

ABI-H0731 (vebicorvir) with NA
HBeAg +ve treatment naïve patients

HBV viral transcripts
(max reduction from baseline for individuals)



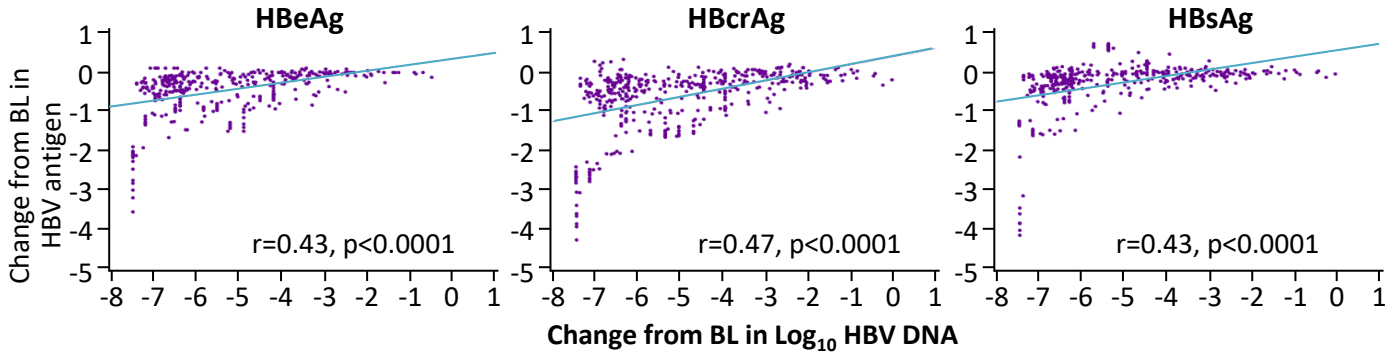
Yuen MF, et al. EASL dILC2020. #LBP30

Changes in viral antigens are more strongly associated with HBV pgRNA than HBV DNA in studies of vebicorvir and NRTI in treatment-naive patients

Aim: To correlate levels of HBeAg, HBcrAg, and HBsAg with changes in HBV DNA and HBV pgRNA during treatment with vebicorvir (VBR) + ETV combination therapy

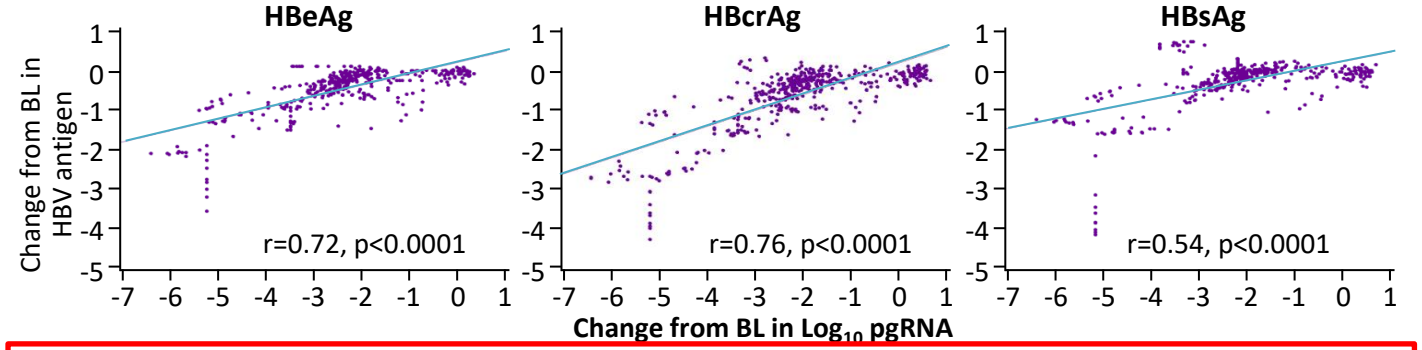
HBV DNA

- **Moderate correlations between HBV DNA and viral antigens**

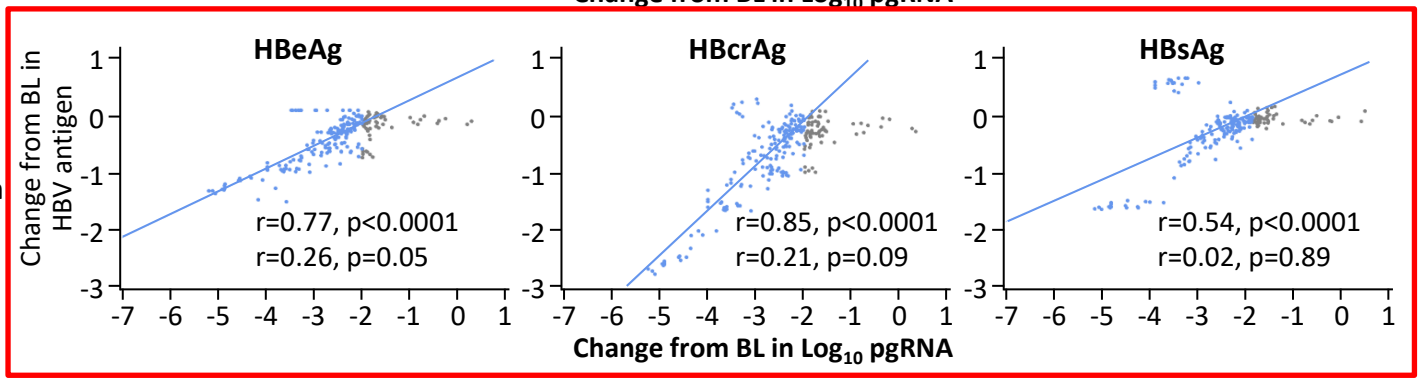


pgRNA

- **High level of correlation between pgRNA and HBeAg, HBcrAg, less with HBsAg**



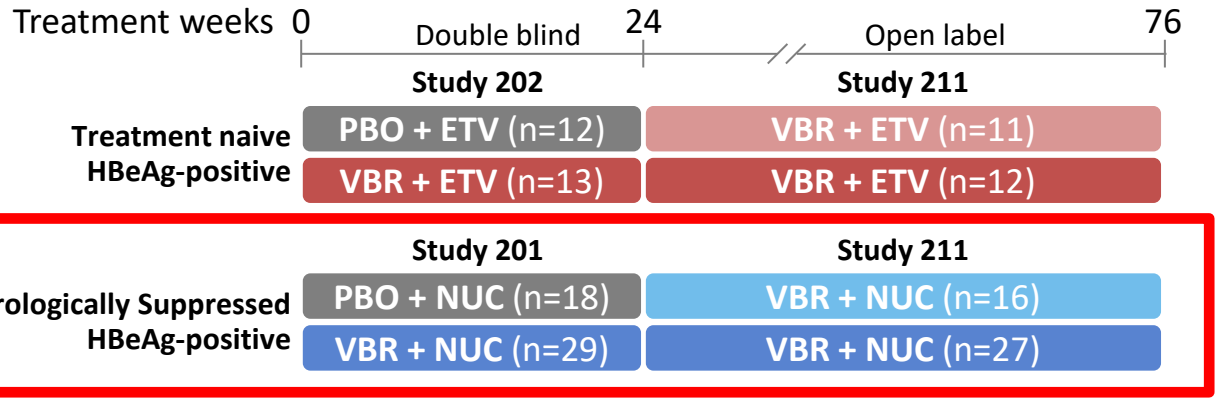
- **High levels of correlation by Pearson coefficient between pgRNA and viral antigen reductions seen only with >2 Log_{10} decline in pgRNA**

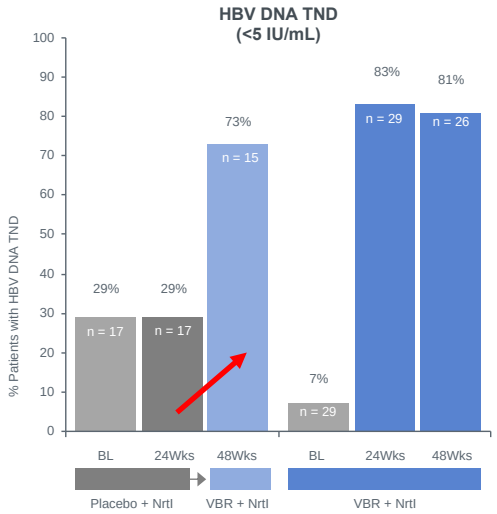


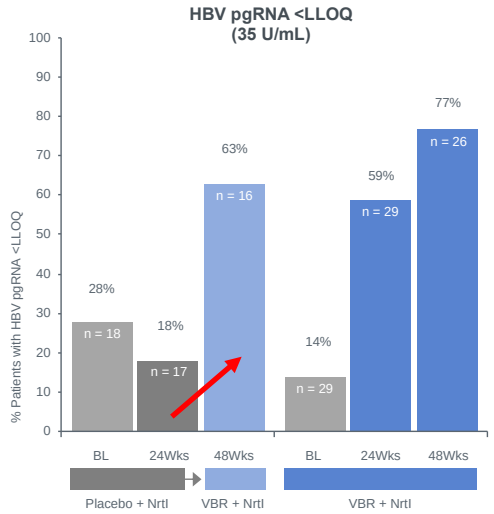
Sulkowski M, et al. AASLD TLMdX2020. #LP37

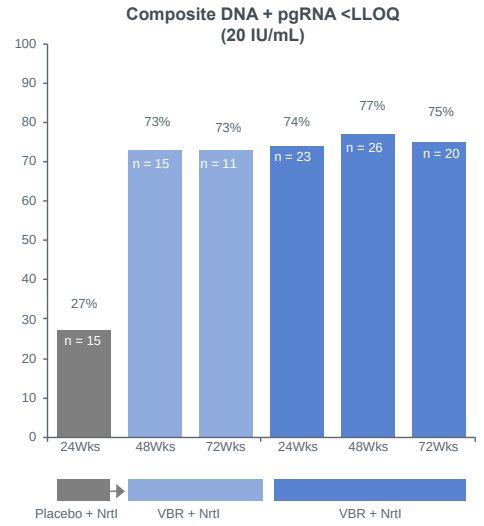
ABI-H0731 (vebicorvir) administered with NA

HBeAg +ve virologically suppressed patients



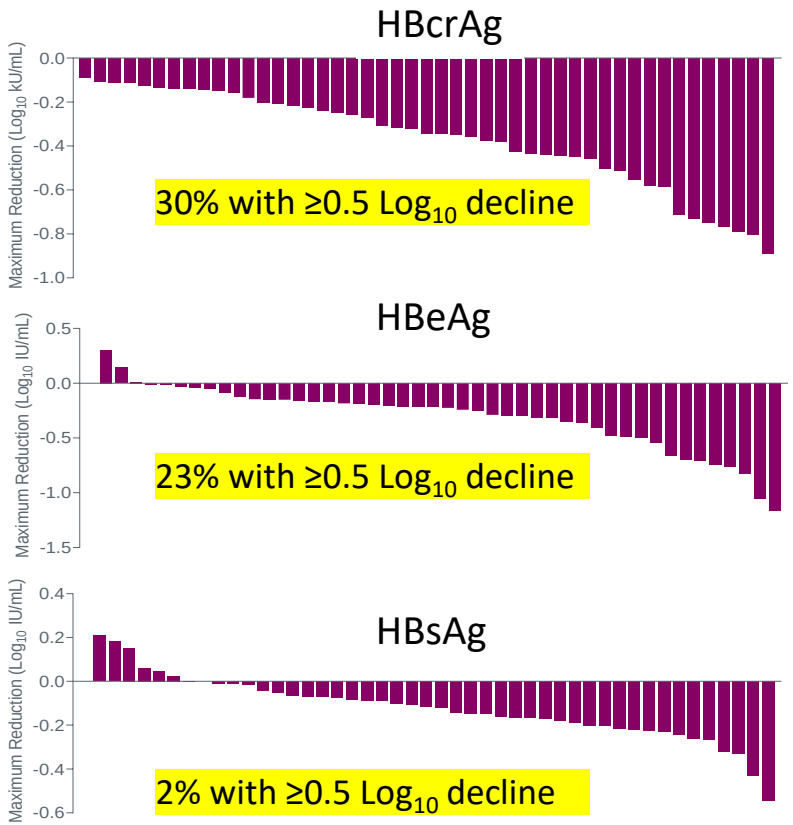






HBV viral transcripts

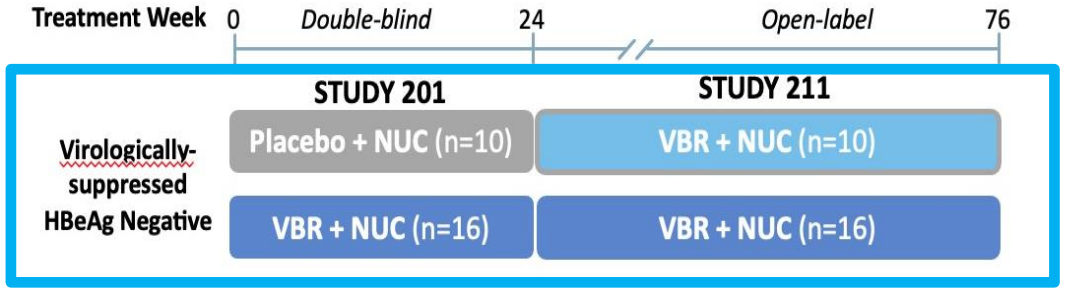
(max reduction from baseline for individuals)

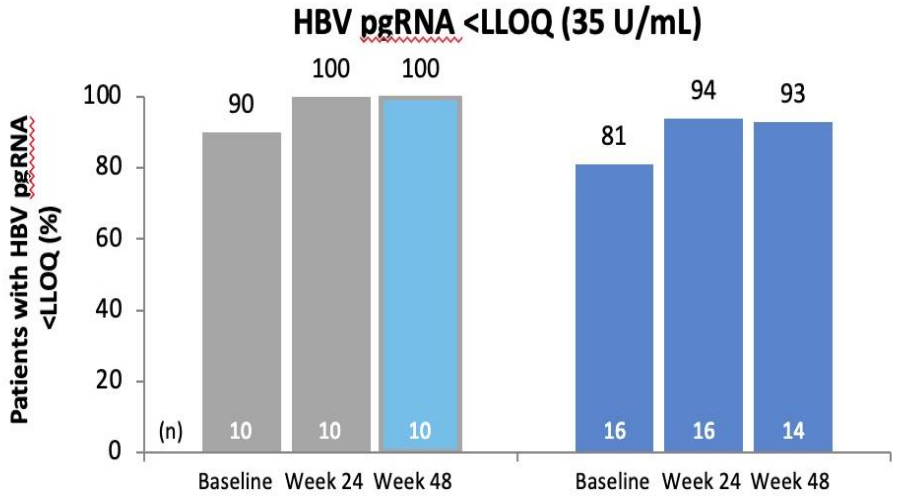


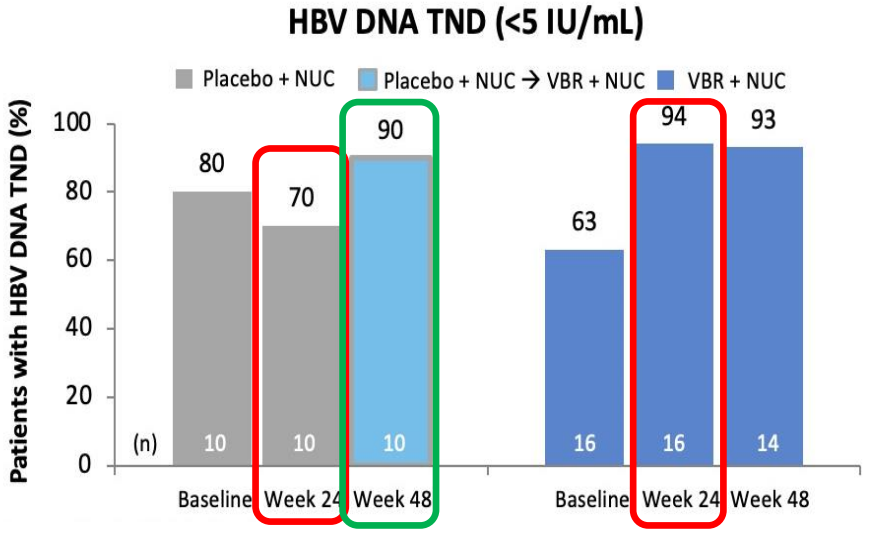
Yuen MF, et al. EASL dILC2020. #LBP30

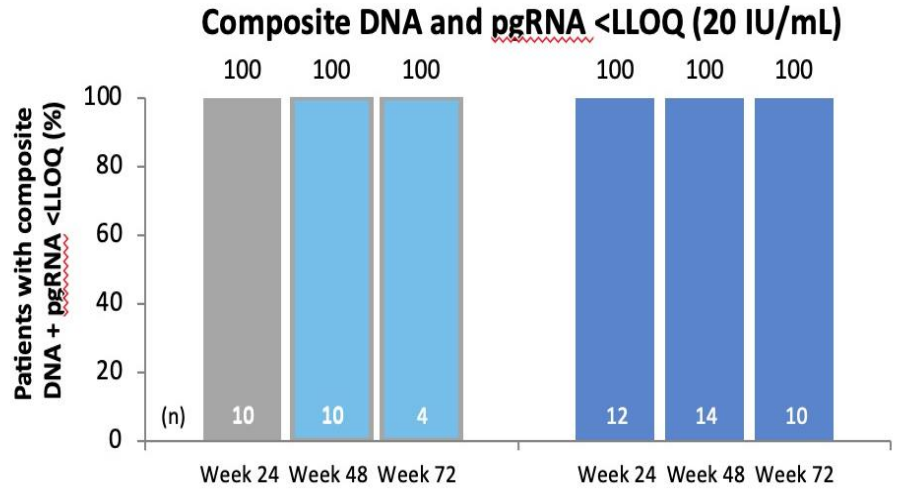
ABI-H0731 (vebicorvir) administered with NA

HBeAg -ve virologically suppressed patients









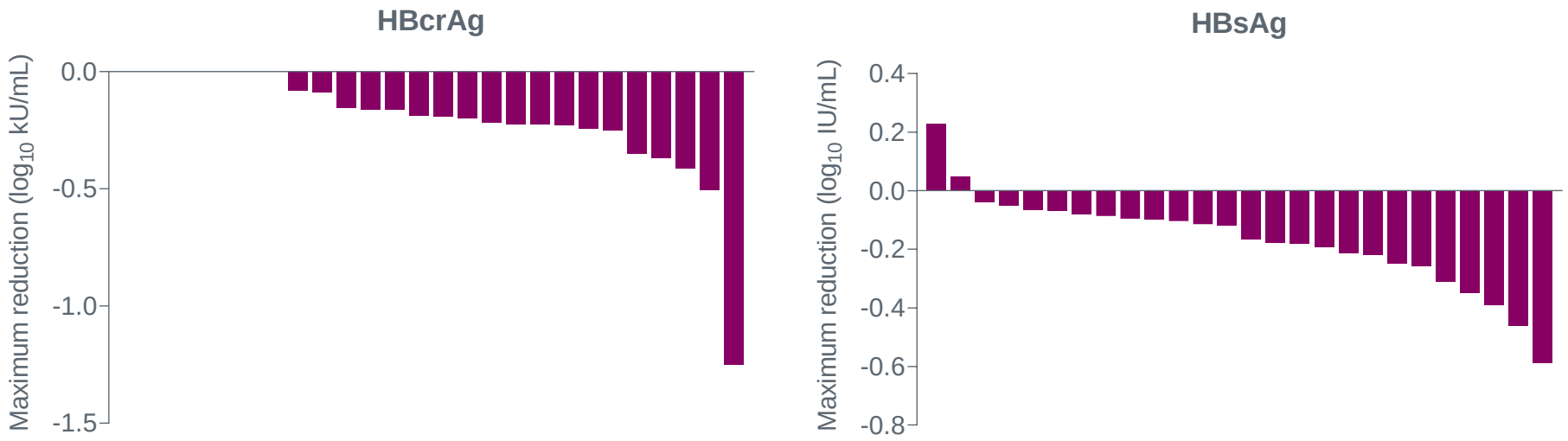
Fung S, et al. EASL dILC 2020, #070

ABI-H0731 (vebicorvir) administered with NA

HBeAg -ve virologically suppressed patients

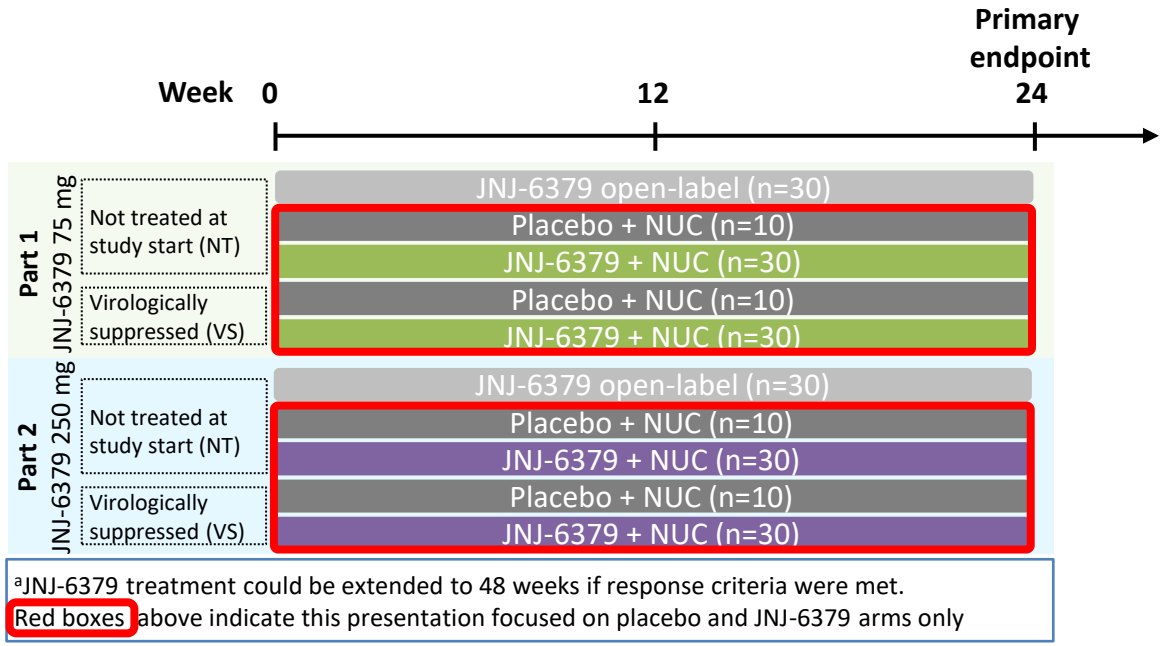
HBV viral transcripts

(max reduction from baseline for individuals)



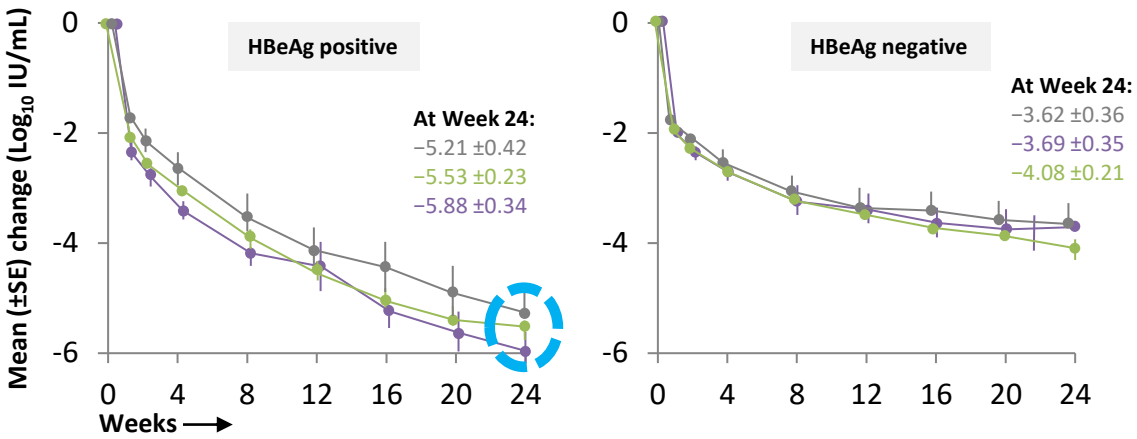
Fung S, et al. EASL dILC 2020, #070

JNJ-56136379 (JADE study): week 24



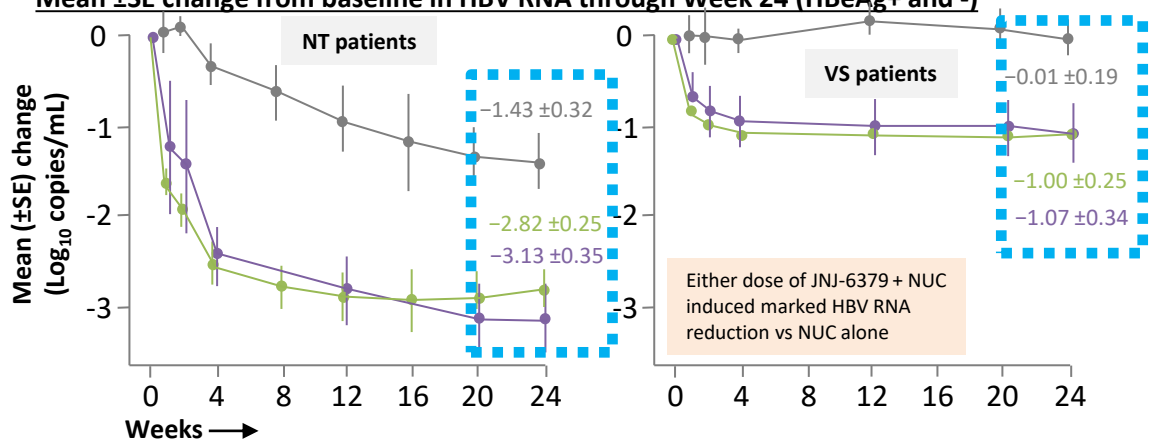
[a]JNJ-6379 treatment could be extended to 48 weeks if response criteria were met.
Red boxes above indicate this presentation focused on placebo and JNJ-6379 arms only

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 -)



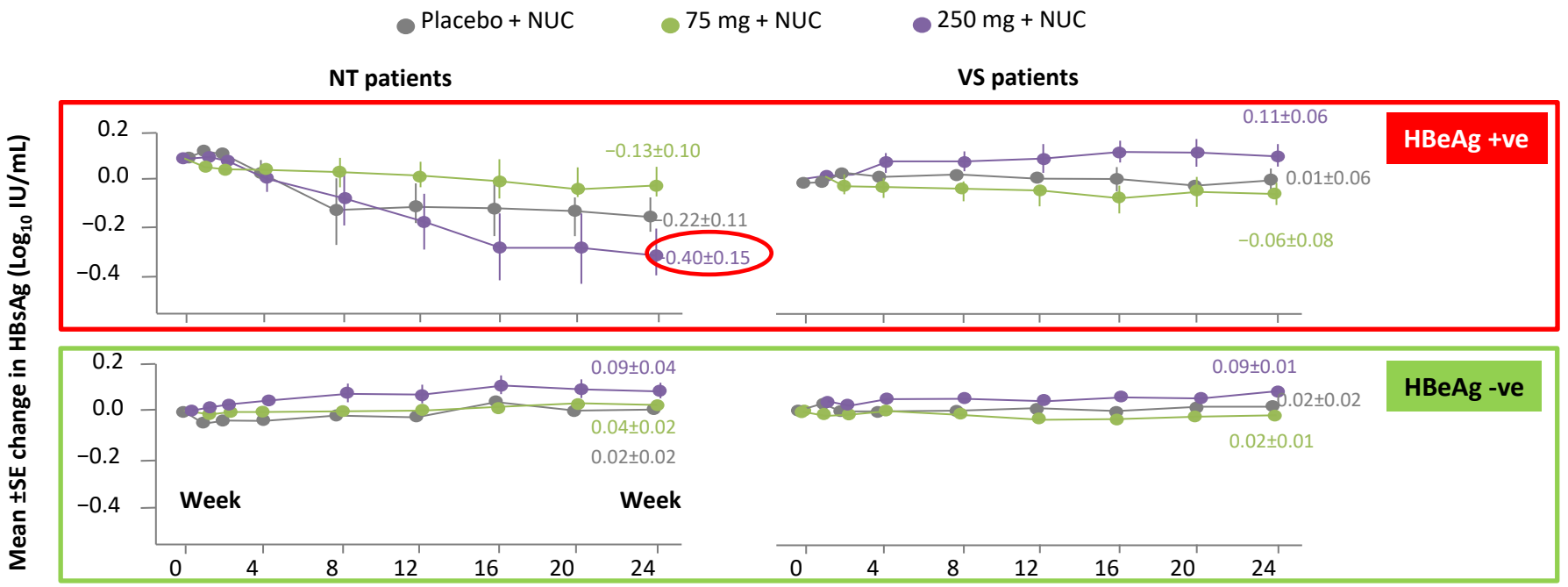
HBV RNA TND, n (%)	JNJ-6379 75 mg + NUC	JNJ-6379 250 mg + NUC	Placebo + NUC
BL	2 (7)	3 (11)	3 (14)
Week 24	16 (59)	19 (76)	9 (45)

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

JNJ-56136379 (JADE study): week 24

Change from baseline in HBsAg at Week 24 by patient population



- JNJ-6379 dose-related decline in HBsAg in treatment-naive HBeAg+ patients (upper left)
- No significant HBsAg declines in other groups

HBsAg reduction from baseline at Week 24, n (%)	NT HBeAg+ patients		
	JNJ-6379 75 mg + NUC	JNJ-6379 250 mg + NUC	Placebo + NUC
>0.3 Log_{10} IU/mL	4 (33)	4 (36)	1 (13)
>0.5 Log_{10} IU/mL	0	4 (36)	1 (13)
Patients with HBsAg >ULOQ at baseline, n	2	2	1

Janssen H, et al. EASL dILC2020. #LBP12

JNJ-56136379 (JADE study): week 24

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 250 mg monotherapy with non-response (<1 Log_{10} IU/mL decline from baseline at Week 4) had subsequent VBT

Janssen H, et al. EASL dILC2020. #LBP12

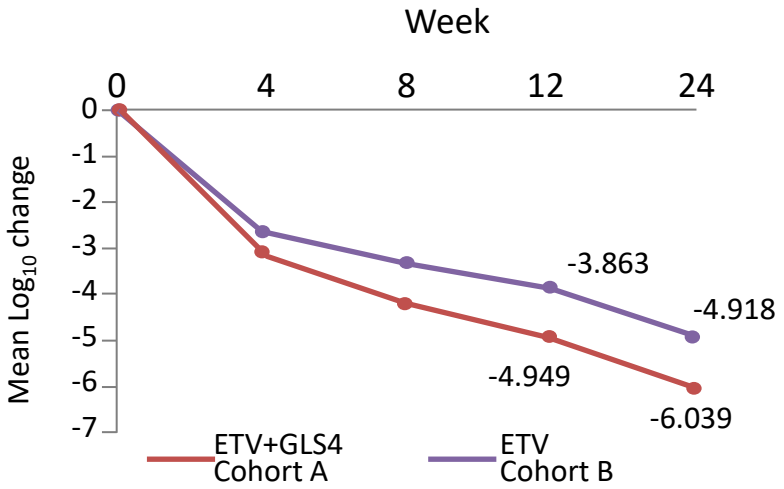
CAM resistant strain: T33N

- 85 fold change in EC_{50}
- 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

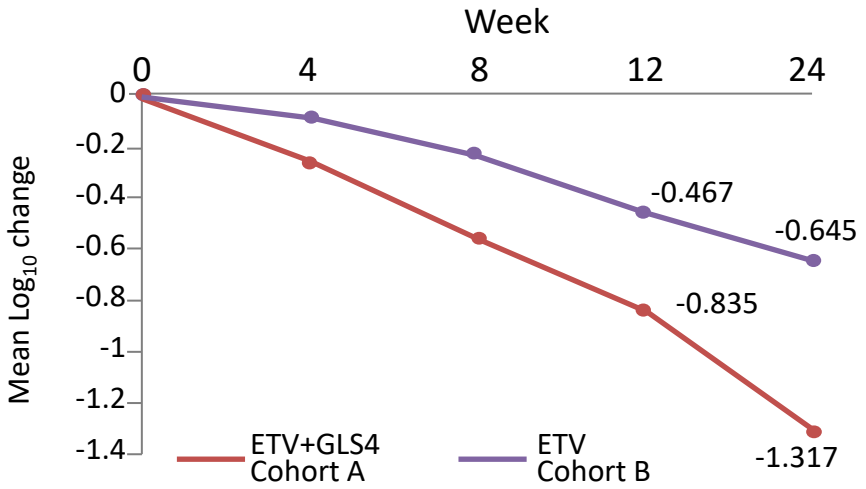
Verbinnen T, et al. EASL dILC2020. # 856

GLS4/ritonavir with entecavir in HBeAg+ patients: week 24

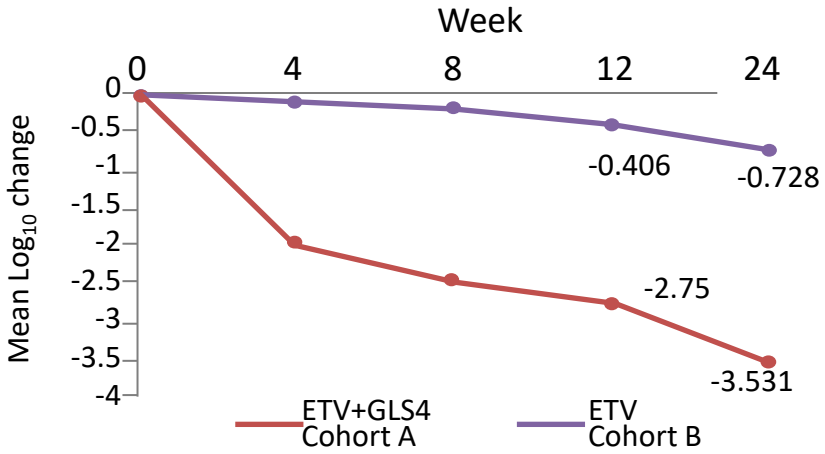
Mean HBV DNA reduction in TN pts



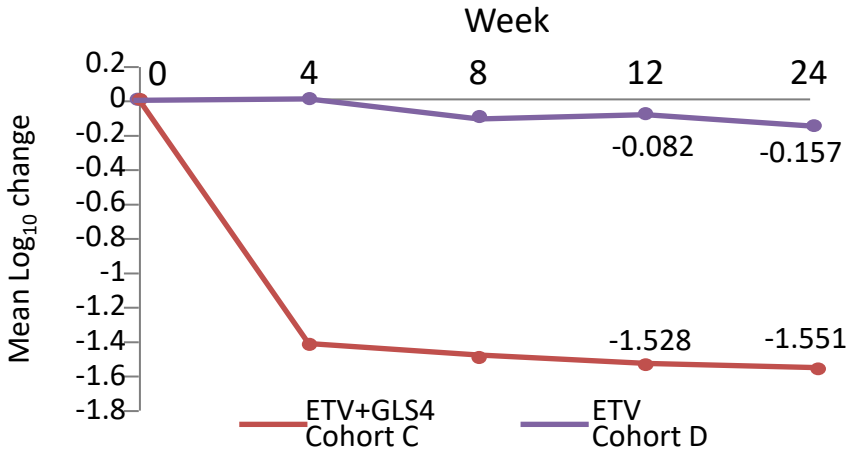
Mean HBcrAg reduction in TN pts



Mean HBV pgRNA reduction in TN pts



Mean HBV pgRNA reduction in VS pts



Zhang M, et al. EASL dILC2020. #452

GLS4/ritonavir with entecavir in HBeAg+ patients: week 24

Mean HBsAg reduction

	GLS4/r + ETV	ETV
Treatment-naive group	**Cohort A (n=32)**	**Cohort B (n=21)**
≥0.5 Log, n (%)	15 (46.9)	6 (28.6)
≥1.0 Log, n (%)	9 (28.1)	3 (14.3)
≥1.5 Log, n (%)	3 (9.4)	0
≥2 Log, n (%)	1 (3.1)	0
Virally suppressed group	**Cohort C (n=32)**	**Cohort D (n=25)**
≥0.1 Log, n (%)	15 (46.9)	2 (8.0)
≥0.2 Log, n (%)	5 (15.6)	0
≥0.3 Log, n (%)	1 (3.1)	0

Cohort	Mean decline in HBsAg (Log_{10} IU/mL)	Mean decline in HBeAg (Log_{10} IU/mL)
A	0.69	0.89
B	0.40	0.58
C	0.10	0.23
D	0.05	0.14

Mean declines in HBsAg and HBeAg greater with GLS4 + ETV vs ETV alone: Cohorts A (TN) and Cohort C (VS)

Zhang M, et al. EASL dILC2020. #S452

Upcoming CAMs: EDP-514

In Vivo Efficacy in Humanized Mouse Model

- Treatment of HBV infected human liver-chimeric mice (PXB mice) with EDP-514 for 12 weeks resulted in a time and dose-dependent viral load reduction.
- The maximum HBV DNA reduction from baseline was 2.99, 3.61, 3.95 and 4.43-log_{10} with EDP-514, given orally at 25, 50, 75 and 100 mg/kg BID, respectively.
- EDP-514 treatment also led to >3-log_{10} reduction in circulating HBV RNA, whereas entecavir had no effect.
- There was a small but significant reduction in HBsAg (max 0.38-log_{10} at 100 mg/kg) and HBeAg (max 0.43-log_{10} at 100 mg/kg BID) in mice treated with EDP-514.
- The virus rebounded to baseline after withdrawal of treatment.

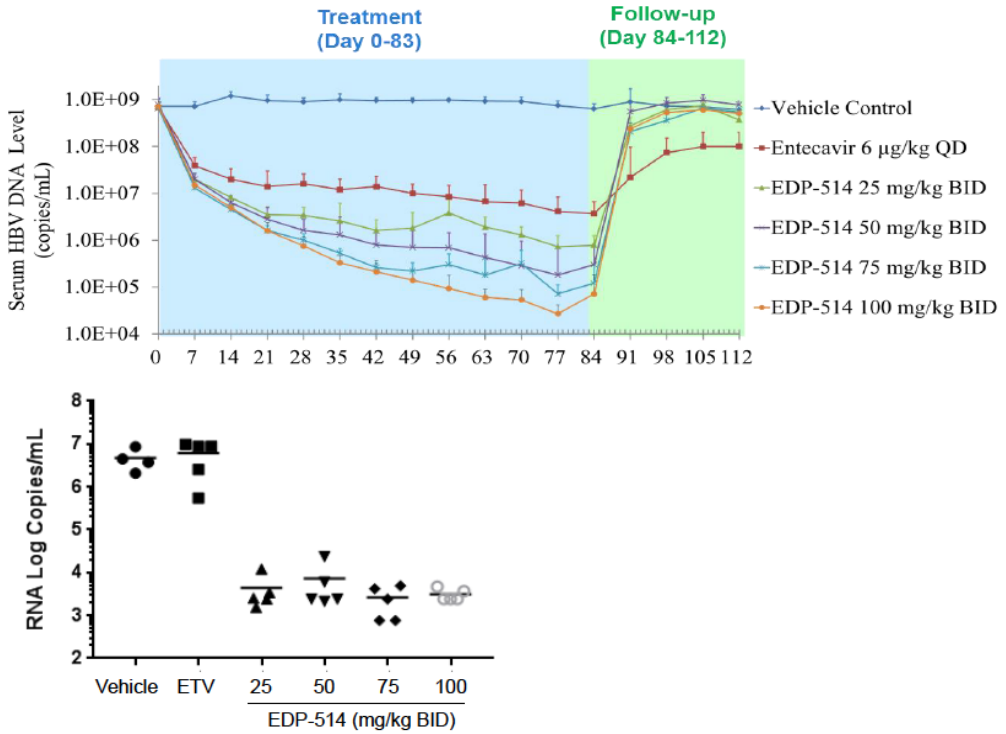


Figure 6. HBV RNA level on Day 70

Activity Against RT and Core Mutants

- EDP-514 is fully active against known nucleos(t)ide reverse transcriptase inhibitor (NRTI) resistance mutations.
- Among HBV core mutations previously reported resistant to treatment with other core inhibitors, only T33N and Y118F significantly affect susceptibility to EDP-514.

Mutations in RT	EC_{50} (nM)	Fold Shift
WT	11	-
M204I	52	4.7
M204V+L180M	25	2.3
M204V+L180M+V173L	16	1.5
M204V+L180M+V173L+M250V+I169T	22	2.0
M204V+L180M+V173L+N236T	26	2.4
N236T	25	2.3
N236T+A181T	14	1.3

Table 5. Activity against HBV reverse transcriptase (RT) mutants.

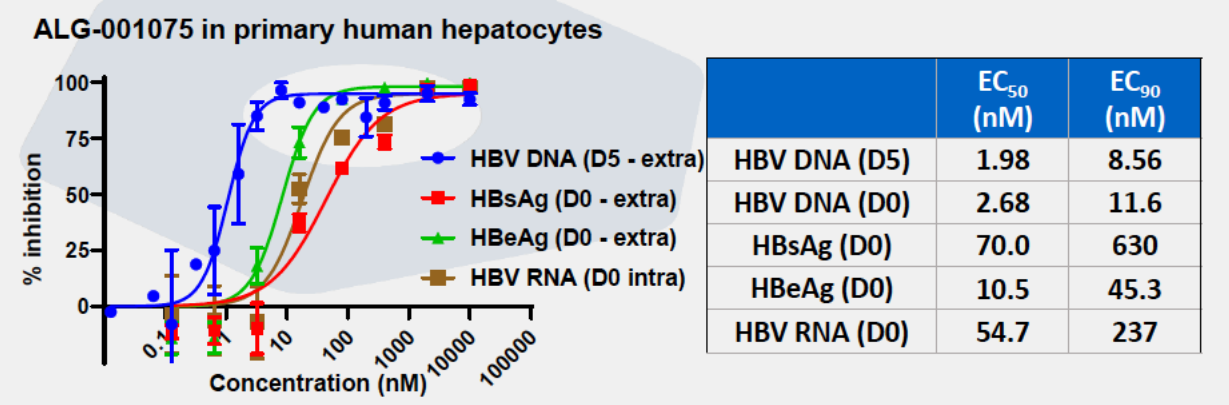
Mutations in Core	EC_{50} (nM)	Fold Shift
WT	13	-
D29G	43	3.3
T33N	2937	226
S106T	8	0.6
T109I	5	0.4
T109M	13	1
Y118F	236	18.2
V124F	56	4.3

Table 6. Activity against HBV core mutants.

HBV genomes containing mutations were synthesized in vitro, transfected into HepG2 cells to produce mutant viruses, and then tested for susceptibility to EDP 514.

Vaine M, et al. EASL 2019 #191

Upcoming CAMs: ALG-000184 (prodrug of ALG-001075)



	EC_{50} (nM)	EC_{90} (nM)
HBV DNA (D5)	1.98	8.56
HBV DNA (D0)	2.68	11.6
HBsAg (D0)	70.0	630
HBeAg (D0)	10.5	45.3
HBV RNA (D0)	54.7	237

Zhang QL, et al. EASL 2020: #2889

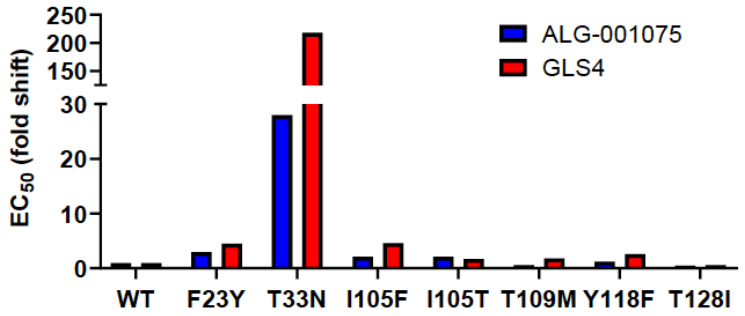
Table 2: Antiviral activity of ALG-001075 and nucleos(t)ide inhibitors tenofovir disoproxil fumarate (TDF), entecavir (ETV), and lamivudine (3TC) against known nucleos(t)ide resistance mutations. Resistance testing was performed as described in Figure 2. Green shading indicates no or minimal shift (<3X), orange moderate shift (5 to 20x) and red substantial shift (> 20x).

	ALG-001075	TDF	ETV	3TC
	EC50 (fold shift)			
Wildtype	1.0	1.0	1.0	1.0
rtN236T	1.3	2.9	ND	ND
rtM204I	1.3	5.8	ND	ND
rtL180M+M204V+M250V+I169T	2.3	ND	247	368
rtL180M+M204V+T184G+S202I	2.1	1.1	>450	>45

Table 1: Antiviral activity and cytotoxicity of ALG-001075 and its prodrug ALG-000184 compared with reference CAMs in HepG2.2.15 and HepG2.117 cells

Compound	HepG2.2.15			HepG2.117		
	EC_{50} (nM)	EC_{90} (nM)	CC_{50} (nM)	EC_{50} (nM)	EC_{90} (nM)	CC_{50} (nM)
ALG-001075	0.53 ± 037	1.84 ± 1.39	> 500	0.63 ± 0.39	3.17 ± 3.44	> 500
ALG-000184	ND	ND	ND	1.37 ± 0.73	4.98 ± 1.61	> 500
GLS4	3.52 ± 0.61	11.6 ± 5.30	> 1000	13.4 ± 6.18	48.7 ± 32.3	> 10,000
RO7049389	4.17 ± 0.08	16.5 ± 2.50	> 50,000	61.8 ± 22.1	249 ± 105	> 500
JNJ-632	ND	ND	ND	87.0 ± 25.9	219 ± 57.8	> 50,000
AB-423	ND	ND	ND	54.8 ± 13.5	258 ± 147	46,035

ND: not determined



Jekle A, et al. AASLD 2020: #823

Safety profile of CAM in hepatitis B patients

4 week studies

1) NVR 3-778
- 600mg (higher dose cohort): dry mouth (12.5%)

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

2) ABI-H0731
- Rash (grade 3) in 1 of 2 patients receiving the highest dose 400 mg
- No rash in patients receiving 100 – 300 mg
- Whole group: rash (3%), dizziness (6%)

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

3) RO9389
- Headache: 16%
- ALT increase: 5 out of 31 (grade 2-4)
  all completed 28-day treatment without dose change or interruption, all resolved

  no evidence for association between ALT elevation and drug exposure

Yuen MF, et al. Lancet Gastroenterol Hepatol (in press)

4) JNJ 6379
- Headache (grade 1): 24%
- ALT increase
  grade 2: 2%
  grade 4: 5%

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

Safety profile of CAM in hepatitis B patients

24 week study

JNJ 6379

- TEAE

Most are grade 1 or 2

- ALT increase

grade 3: 3%
grade 4: 5%

Janssen H, et al. EASL dILC2020. #LBP12

72 week study

ABI-H0731

- Rash: 14/95 (15%)
  - 67%: related or possibly related
  - 33%: not related or unlikely related

  All grade 1 except 1 grade 2
  (all resolve without treatment discontinuation)

- ALT increase
  - N=95
  - Grade 1: 8 (8%)
  - Grade 2: 3 (3%)
  - Grade 3: 3 (3%)

  No pattern of increased ALT indicative of hepatotoxicity

Jacobson I, et al. AASLD TLMdX2020. #820

Conclusions

- Effective mode of action has been demonstrated
  - 4 weeks of treatment (primary MOA)
    - HBV DNA reduction of 3 log; HBV RNA reduction of 2.5 log
    - No clinical meaningful viral antigen reduction
    - Better viral suppression when combined with other agent e.g. Peg-IFN
  - > 24 weeks of treatment (? secondary MOA)
    - More profound HBV DNA and HBV RNA reduction when combined with NA
    - Start to demonstrate some viral antigen reductions especially in treatment naïve HBeAg +ve patients
- NA resistant strains remain suppression susceptible by CAM
- Resistant strain (T33N) remains a concern in CAM monotherapy
- Good safe and tolerability profile
  - Monotherapy
  - Combination therapy

Thank you