HBcrAg, HBV-RNA Declines in A Phase 2a Study Evaluating the Multi-Dose Activity of ARB-1467 in HBeAg-Positive and Negative Virally Suppressed Patients With Hepatitis B

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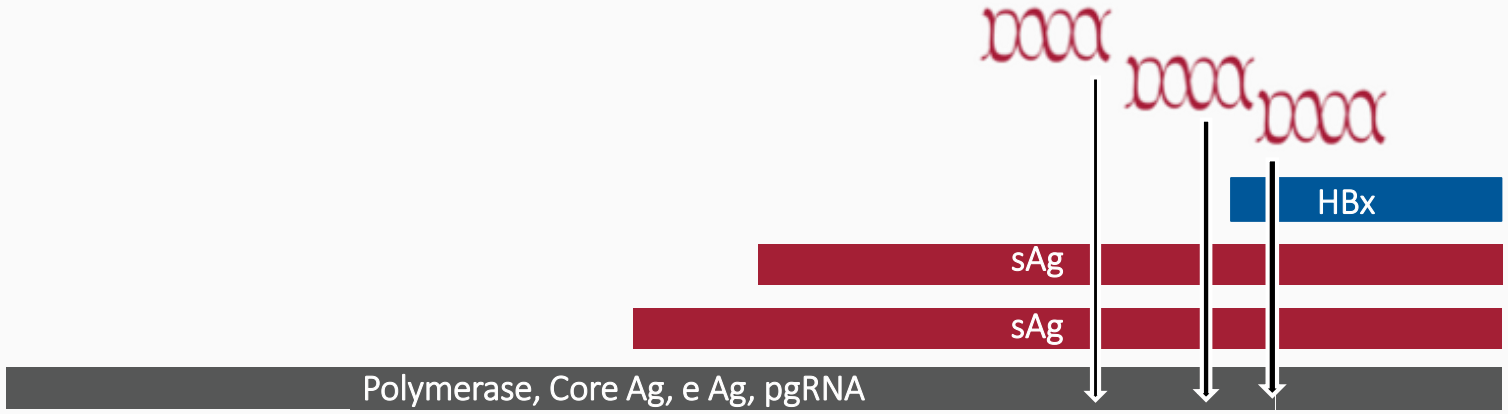
Disclosure

- TBC

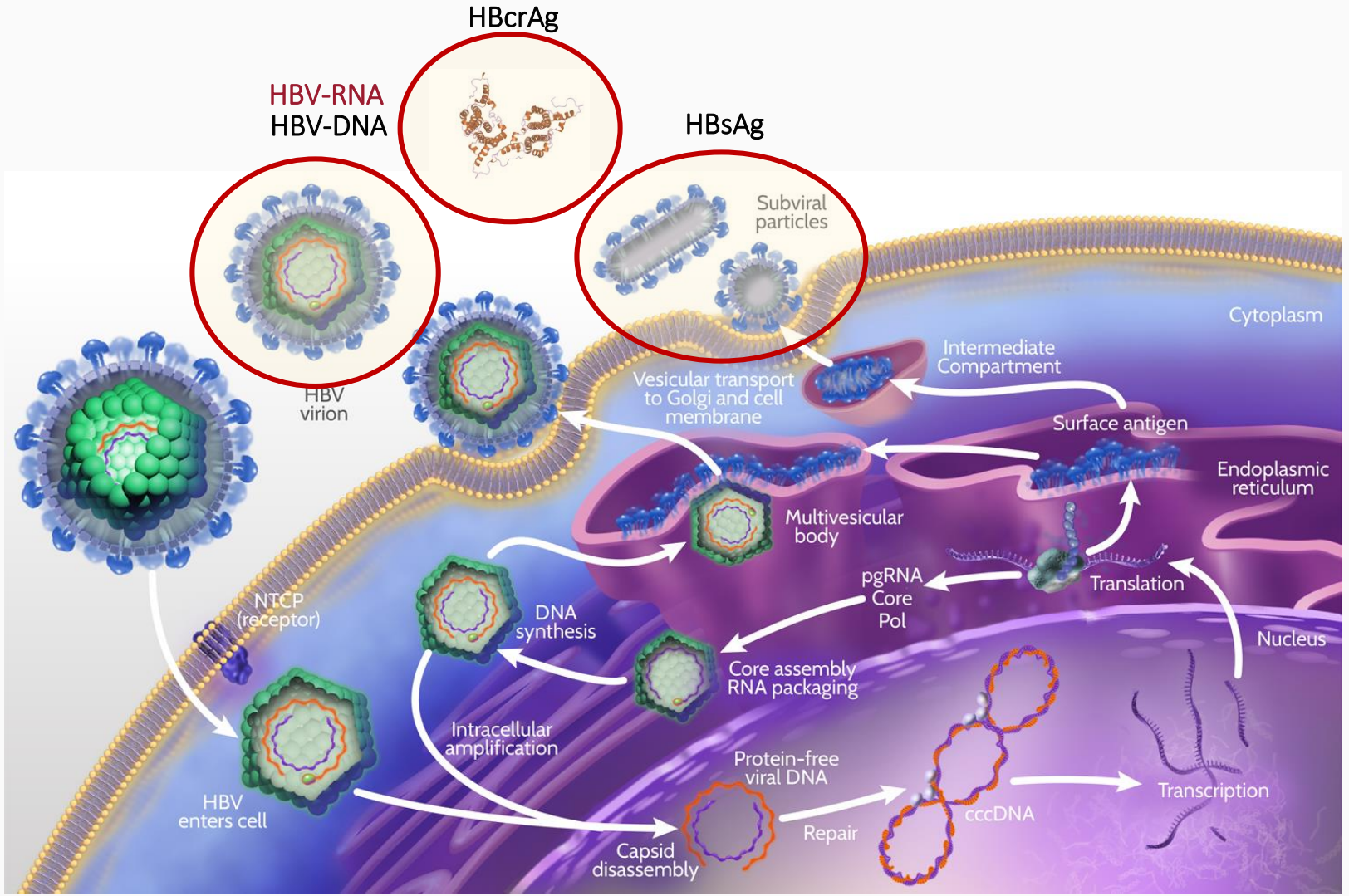
ARB-1467

- Novel RNA interference product
- Unique 3-trigger design inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens
- Delivered via proprietary lipid nanoparticle (LNP) technology
- Generally safe and well tolerated to date



HBV Activity Markers

- HBsAg and HBV-DNA are the standard biomarkers of cccDNA activity
- Significant HBsAg reduction, irrespective of HBeAg status, was seen when ARB-1467 was given to nucleos(t)ide-treated patients in the 002 phase 2 study (NCT02631096)[1]
- Hepatitis B core-related antigen (HBcrAg) and HBV-RNA have also been proposed as biomarkers for cccDNA[2,3]
- We evaluated the correlation between HBsAg, HBcrAg and HBV-RNA levels in the 002 study



1. Streinu-Cercel A, et al. J Hepatol 2017;66(suppl 1):S688–S689; 2. Gao Y, *et al. J Clin Microbiol* 2017;55:2972–2982;
3 Chuaypen N, *et al. Clin Microbiol Infect* 2017 Jul 24 doi: 10.1016/j.cmi.2017.07.016. [Epub ahead of print].

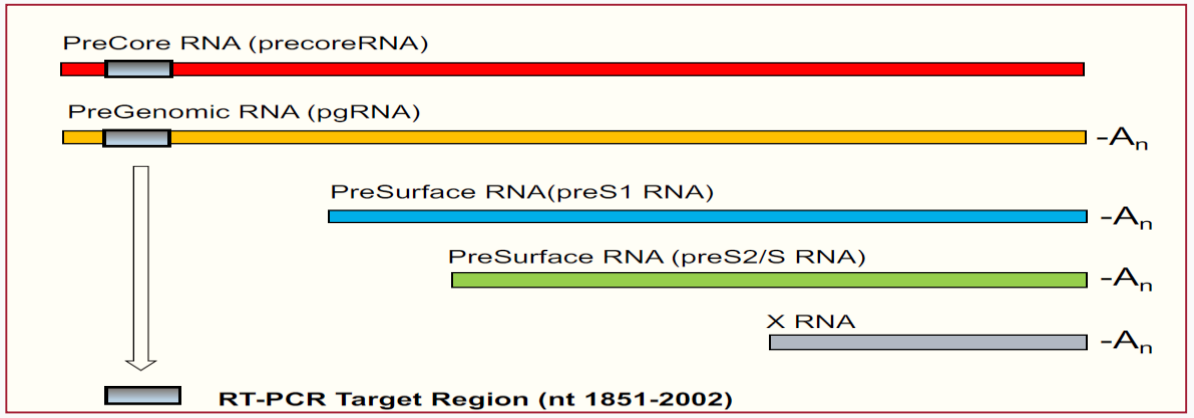
Biomarkers Assessed

Pharmacodynamic Markers

- **HBV-DNA:** COBAS®AmpliPrep / COBAS® TaqMan v2.0 (qPCR)
  - *LOD 20 IU/mL*
- **HBsAg** *(quantitative)*: Architect
  - *LLOQ 0.05 IU/mL*

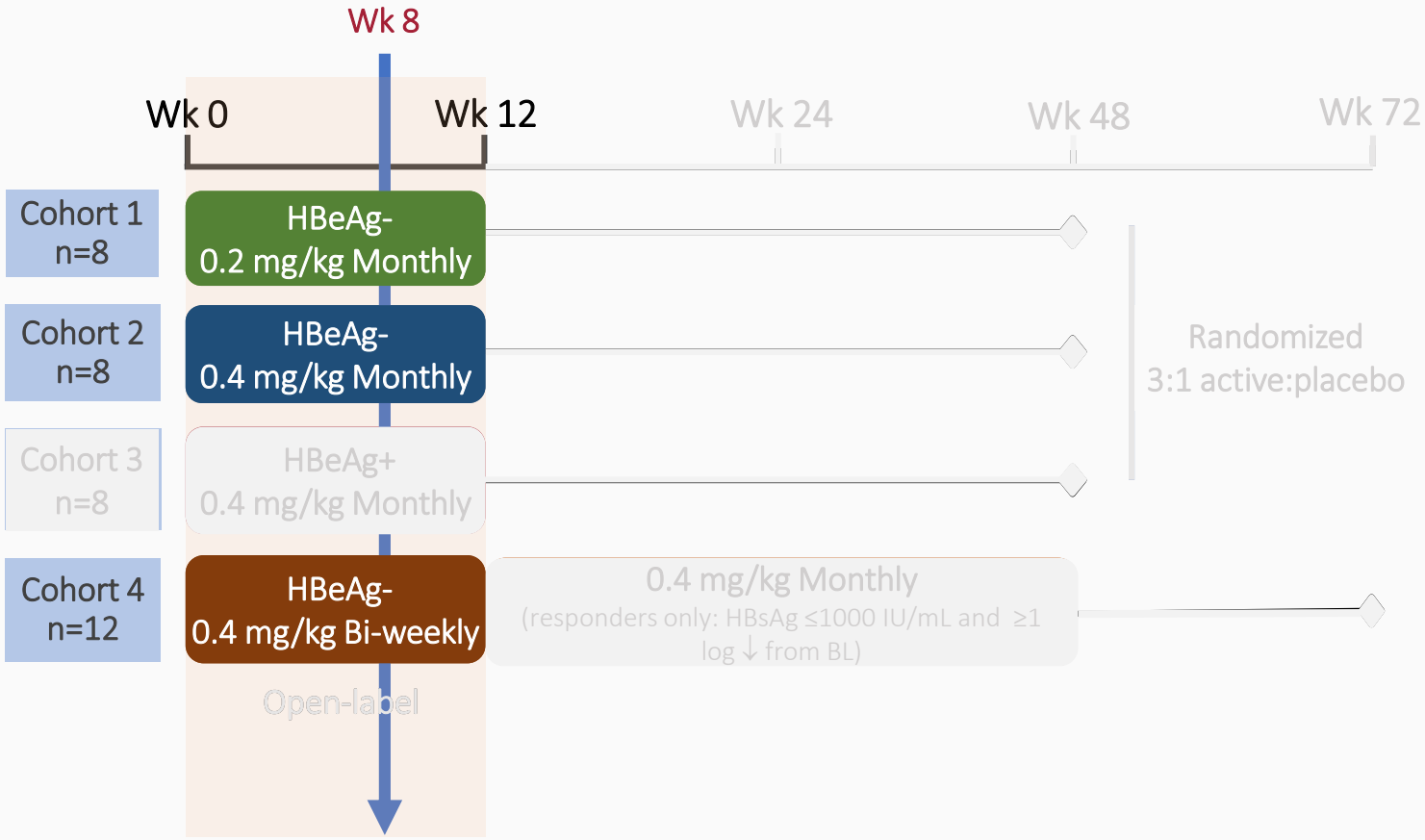
Exploratory Markers

- **HBcrAg:** Lumipulse (Japan)
  - *Dynamic range 3–7 log_{10} IU/mL*
  - *HBeAg, HBcAg and HBV pre-core protein (p22cr) detected*
- **HBV-RNA** *(pre-genomic RNA: pg RNA):*
  Proprietary qRT-PCR methodology (Cenetron Diagnostics)
  - *LLOQ 10 copies/mL*



Study 002 Design

Patients with chronic HBV infection on Stable Nucleos(t)ide Therapy



HBeAg- only

Data collected pre-dose and throughout Weeks 0–10

Last dose at Week 8 (monthly and bi-weekly)

Dosing Schedule:

- Weeks 0, 4 and 8 (monthly)
- Weeks 0, 2, 4, 6, 8 (bi-weekly)

- ARB-1467 or placebo given as a 2-hour IV infusion
- Broad inclusion criteria
  - Non-cirrhotic, chronic HBV infection receiving NA therapy with ETV or TDF for ≥ 12 months
  - HBsAg ≥ 1000 IU/mL, HBV-DNA negative
  - ALT or AST ≤ 2x ULN
  - Fibroscan ≤ 9 kPa
- Pre-medications given the evening prior and 30 minutes prior to each infusion

Patient Baseline Characteristics

Baseline characteristics were similar across cohorts

	Cohort 1	Cohort 2	Cohort 3[a]	Cohort 4	
	HBeAg- 0.2 mg/kg Monthly n=6	HBeAg- 0.4 mg/kg Monthly n=6	HBeAg+ 0.4 mg/kg Monthly n=6	HBeAg- 0.4 mg/kg Bi-weekly n=12	Placebo n=6
Male, *n (%)*	4 (67)	4 (67)	6 (100)	9 (75)	5 (83)
Age, *median (range) y*	44 (28-52)	47 (31-64)	47 (32-52)	49 (29-64)	49 (40-54)
White, *n (%)*	4 (67)	4 (67)	3 (50)	4 (33)	3 (50)
Asian, *n (%)*	2 (33)	2 (33)	2 (33)	6 (50)	2 (33)
BMI, *median (range) kg/m²*	24.6 (21-27)	26.8 (18-30)	28.7 (24-32)	24.2 (18-32)	25.2 (22-27)
ALT, *median (range) IU/mL*	28.5 (19-44)	31.5 (26-78)	38.5 (27-64)	29.5 (13-63)	29.5 (20-45)
HBsAg, *mean (SD) log_{10} IU/mL*	3.5 (0.55)	3.4 (0.72)	3.0 (0.3)	3.6 (0.45)	3.3 (0.44)
HBV-RNA, *mean (SD) log_{10} copies/mL*	1.6 (0.66)	1.2 (0.29)	1.8 (0.95)	1.2 (0.29)	1.7 (0.85)
> LOD (10 copies/mL), *n (%)*	3 (50)	3 (50)	3 (50)	5 (42)	3 (50)
HBcrAg, *mean (SD) log_{10} IU/mL*	3.6 (0.74)	3.2 (0.52)	5.6 (0.44)	3.4 (0.73)	4.0 (1.15)
> LOD (3 log_{10} IU/mL)	4 (67)	3 (50)	6 (100)	8 (67)	5 (83)

Cohort 4 Responder:
HBsAg ≤1000 IU/mL with ≥1 log_{10} decline during the first 10 weeks of treatment

[a]Cohort 3 (HBeAg+) is not included in these analyses.

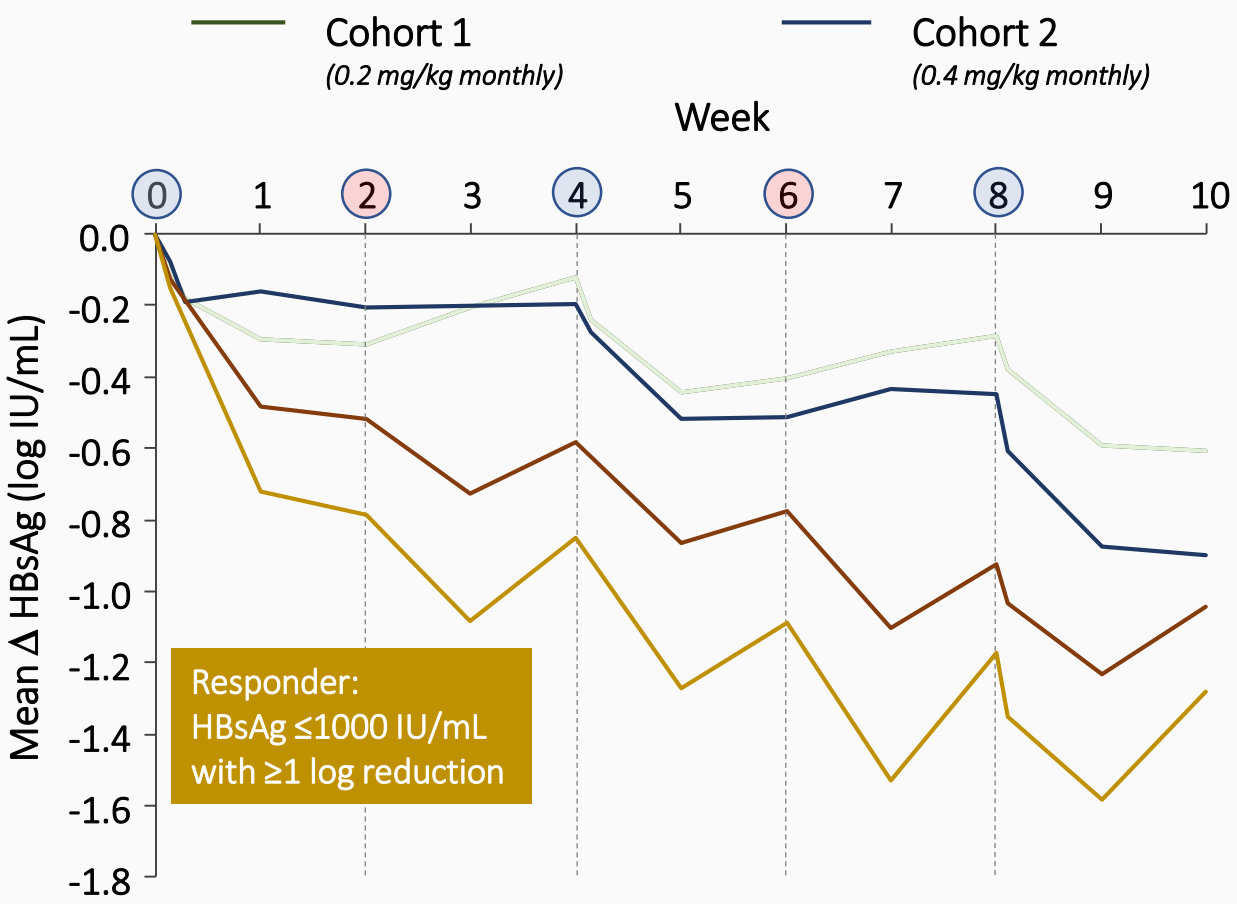
Patient Baseline Characteristics: Genotypes

	Cohort 1	Cohort 2	Cohort 3[a]	Cohort 4	
n (%)	HBeAg- 0.2 mg/kg Monthly n=6	HBeAg- 0.4 mg/kg Monthly n=6	HBeAg+ 0.4 mg/kg Monthly n=6	HBeAg- 0.4 mg/kg Bi-weekly n=12	Placebo n=6
HBV genotype[b]					
B	0	1 (17)	0	1 (8)	0
C	4 (67)	1 (17)	4 (67)	8 (67)	4 (67)
D	2 (33)	3 (50)	0	0	1 (17)
C/D	0	1 (17)	1 (17)	0	1 (17)
Undetermined[c]	0	0	1 (17)	3 (25)	0
IL28B genotype (rs12979860)[d]					
CC	0	0	0	8 (67)	0
CT	0	0	0	1 (8)	0
TT	0	0	0	2 (17)	0
Missing	6 (100)	6 (100)	6 (100)	1 (8)	6 (100)

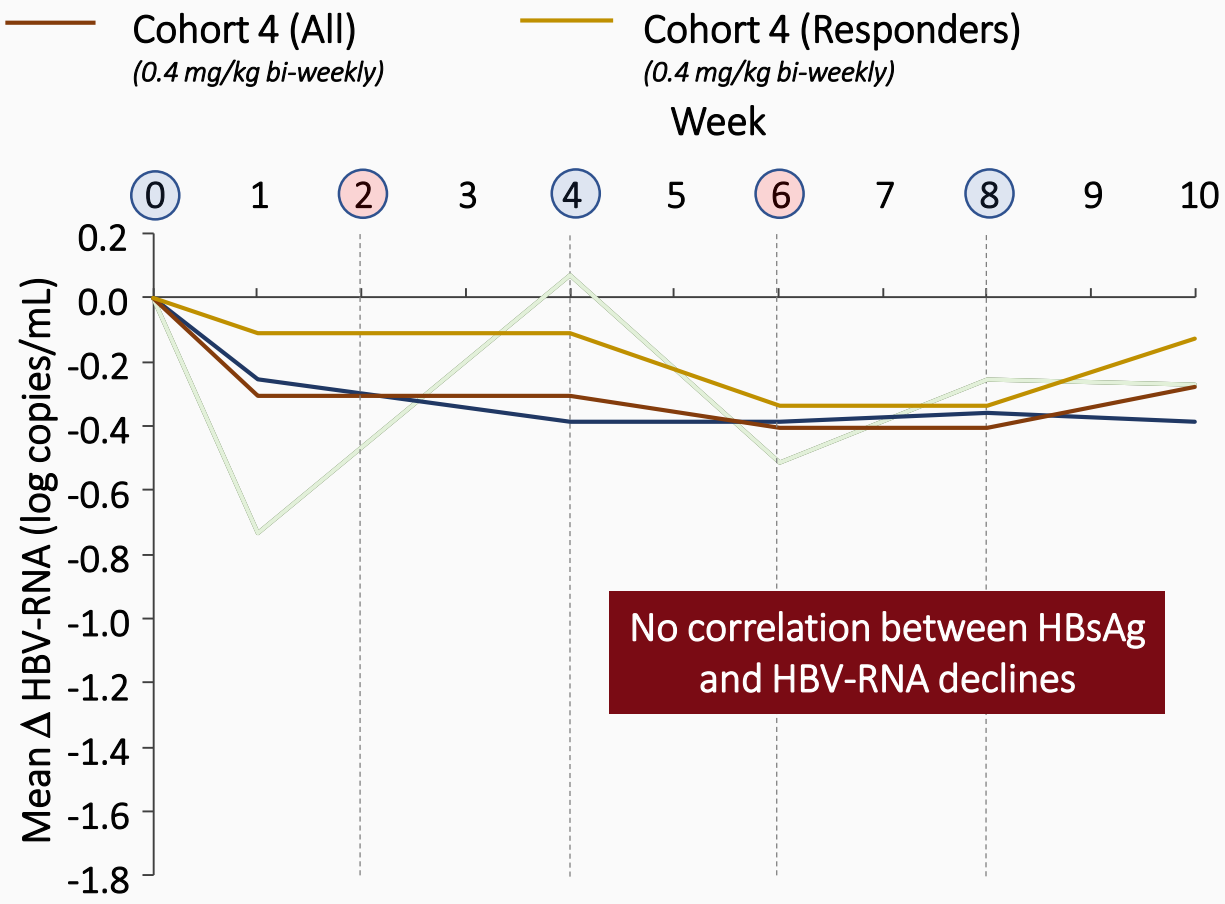
Cohort 4 responder:
HBsAg ≤1000 IU/mL with ≥1 $\log_{10}$ decline during the first 10 weeks of treatment

[a]Cohort 3 (HBeAg+) is not included in these analyses.
[b]HBV genotype line probe assay (INNO-LiPA).
[c]Indeterminate result or unamplifiable sample.
[d]See Presentation LB-17 at this congress

Overall HBsAg and HBV-RNA Declines by Cohort (HBeAg-)



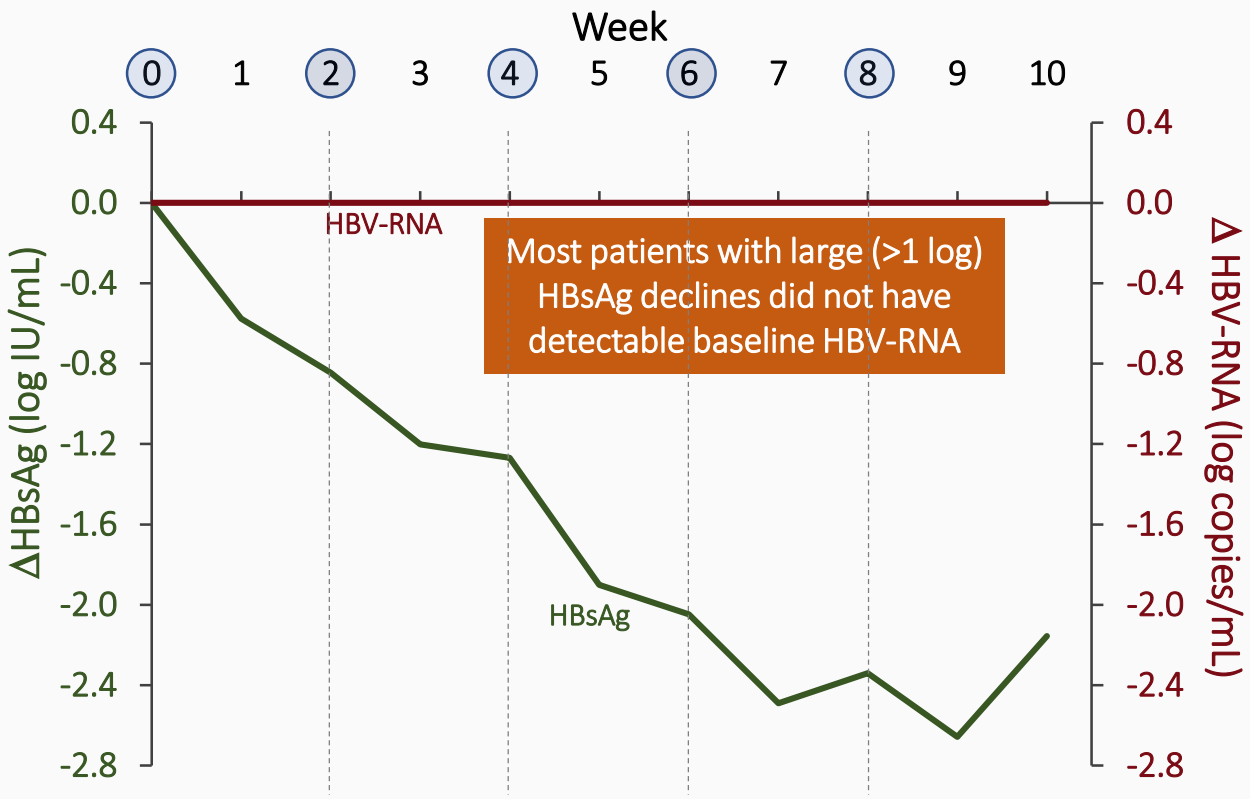
Mean Change from Baseline HBsAg



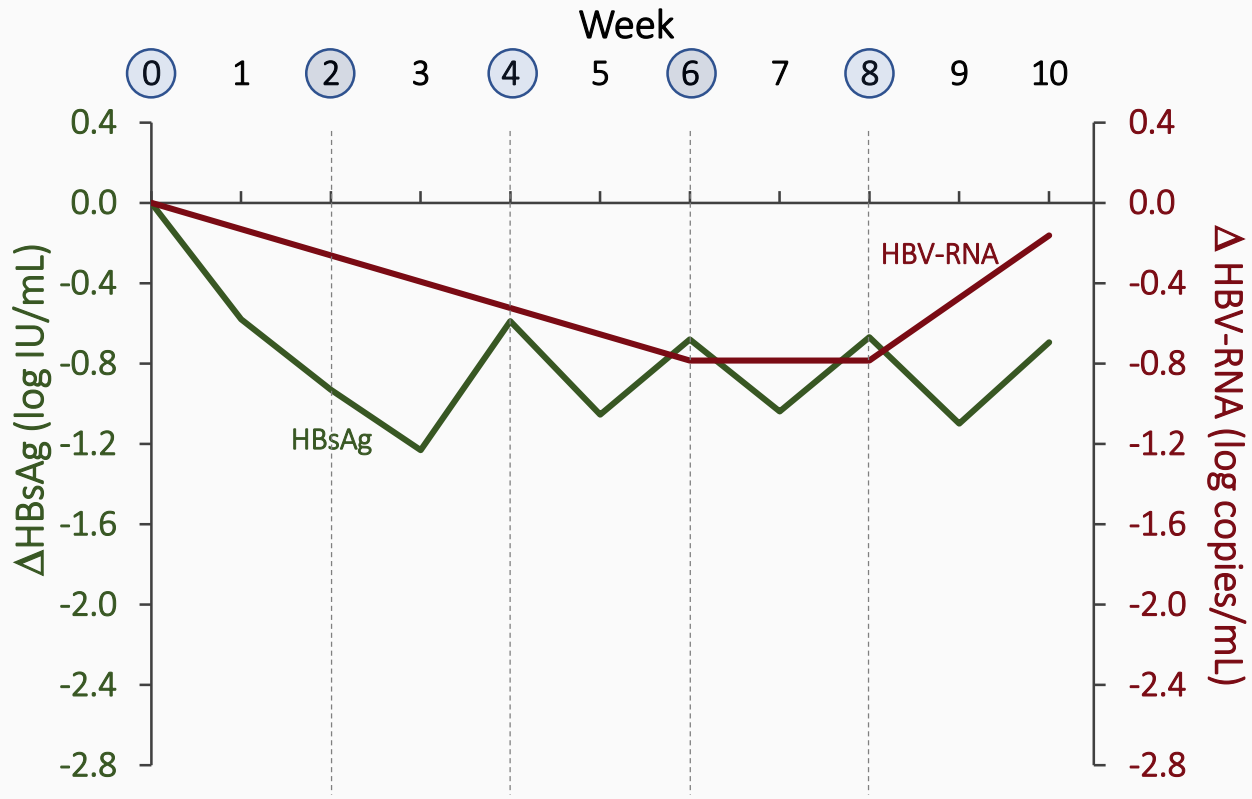
Mean Change from Baseline HBV-RNA

Dosing Day: All Groups Bi-weekly only (Cohort 4)

HBsAg and HBV-RNA in HBeAg- Patients With the Largest Individual Declines (Cohort 4)



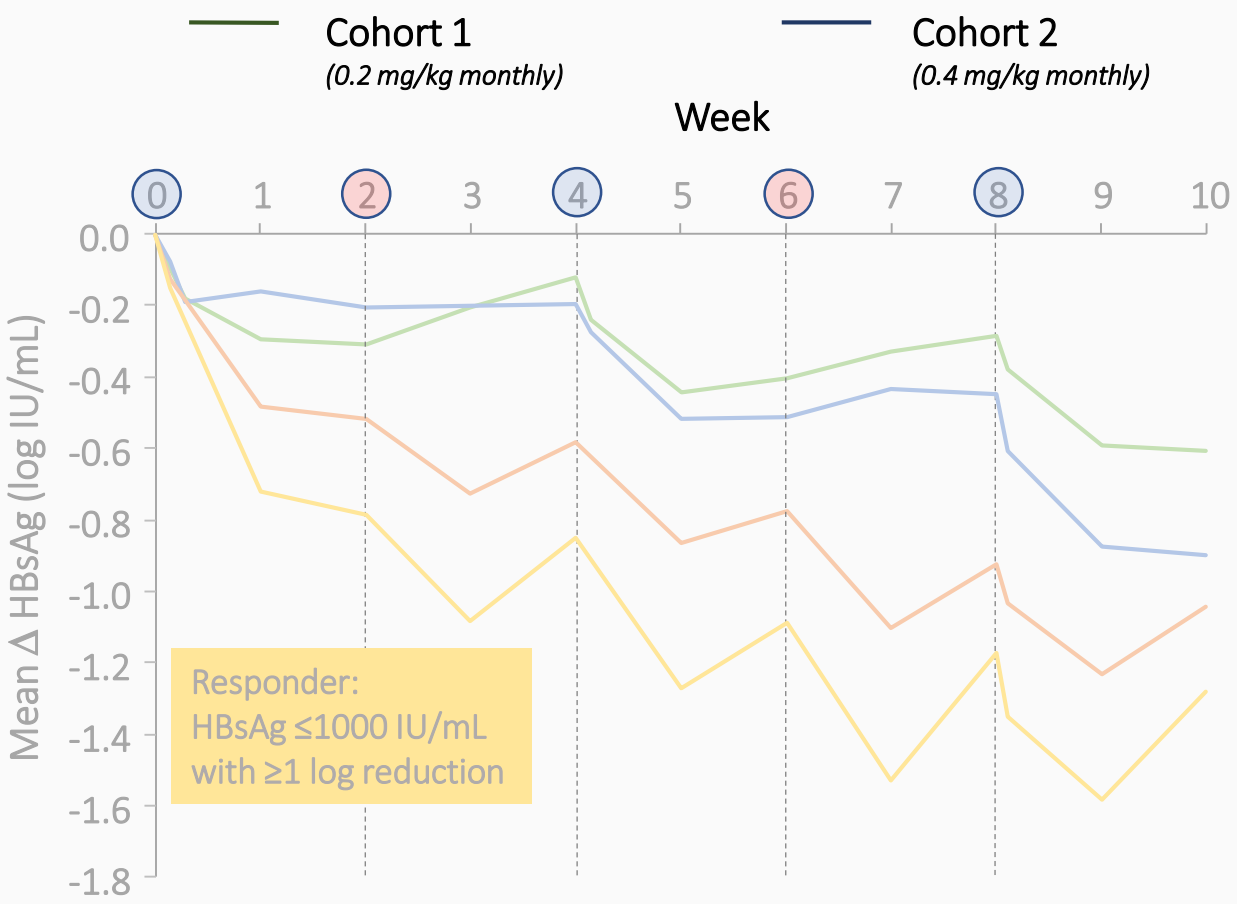
Patient With Largest Individual HBsAg Decline



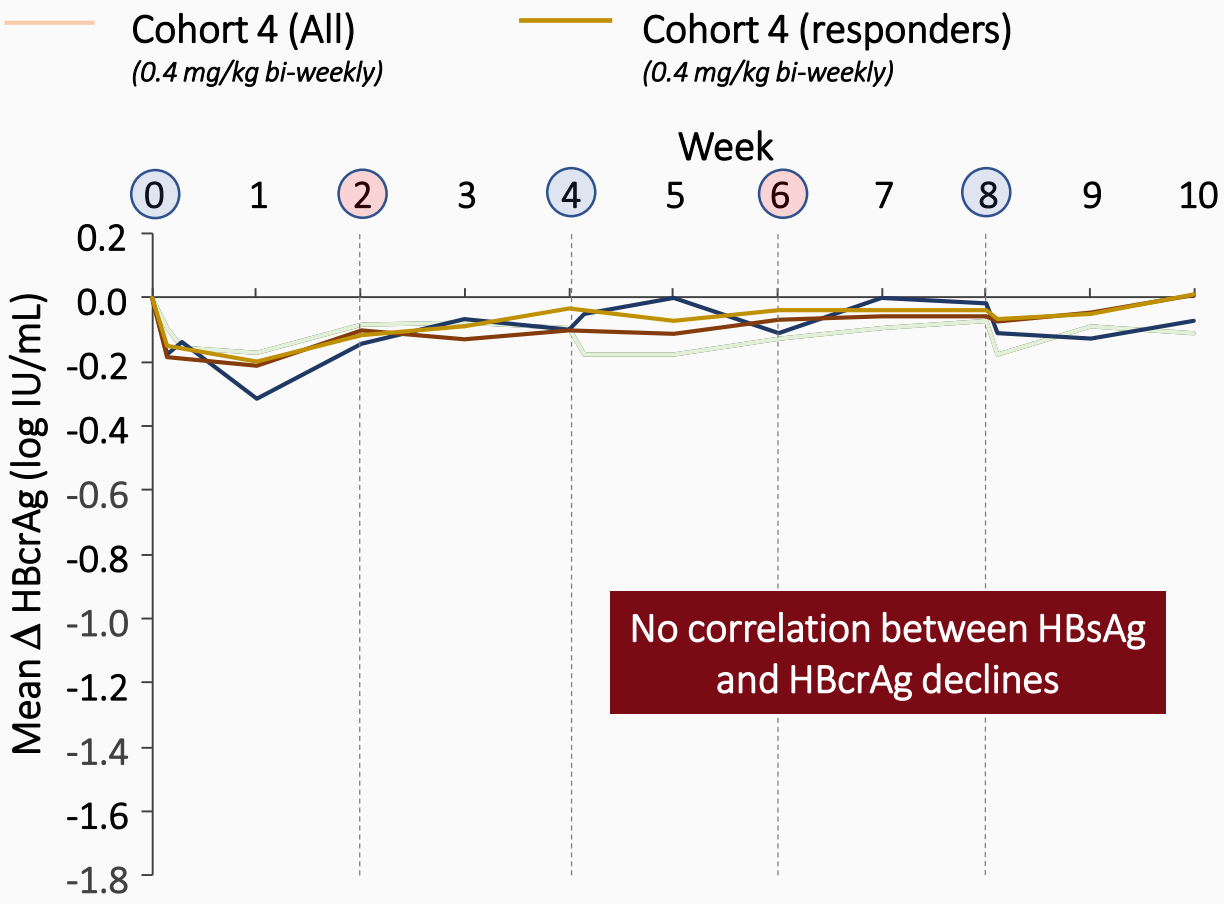
Patient with Largest Individual HBV-RNA Decline

Dosing Day

Overall HBsAg and HBcrAg Declines by Cohort (HBeAg-)



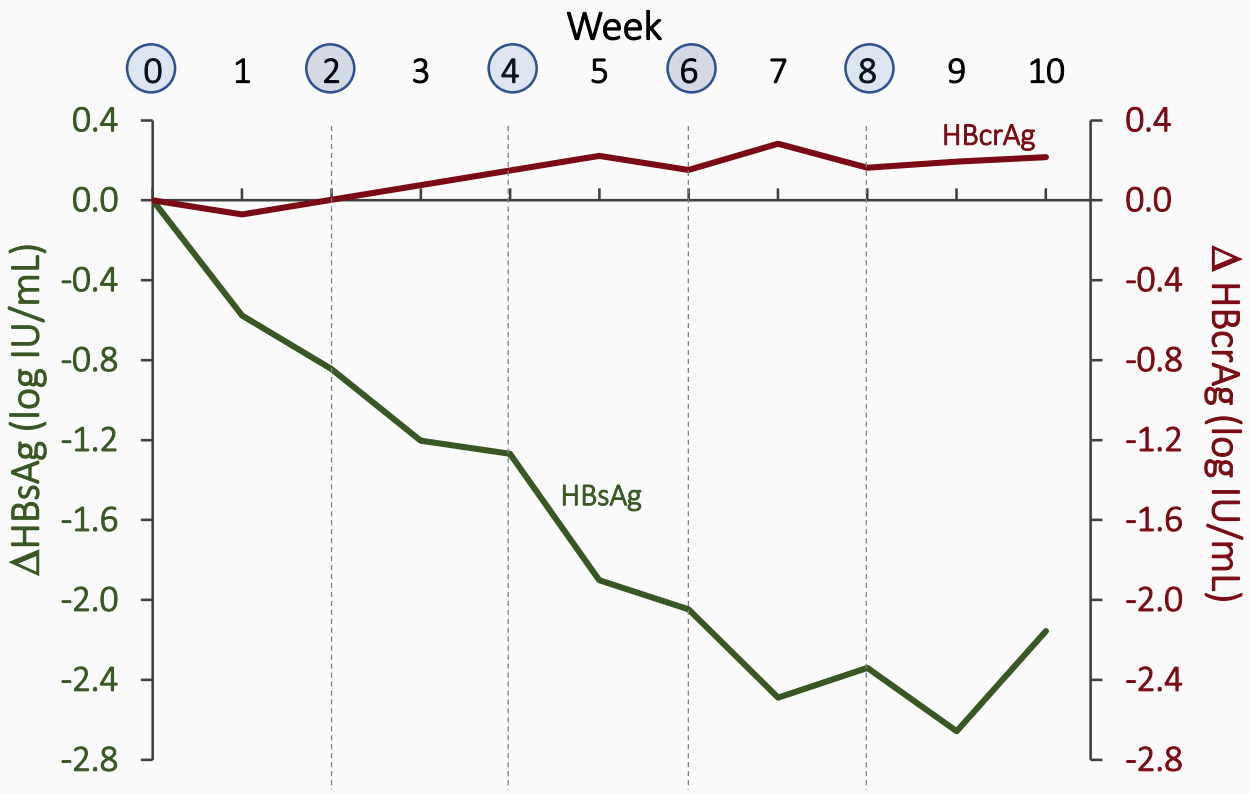
Mean Change from Baseline HBsAg



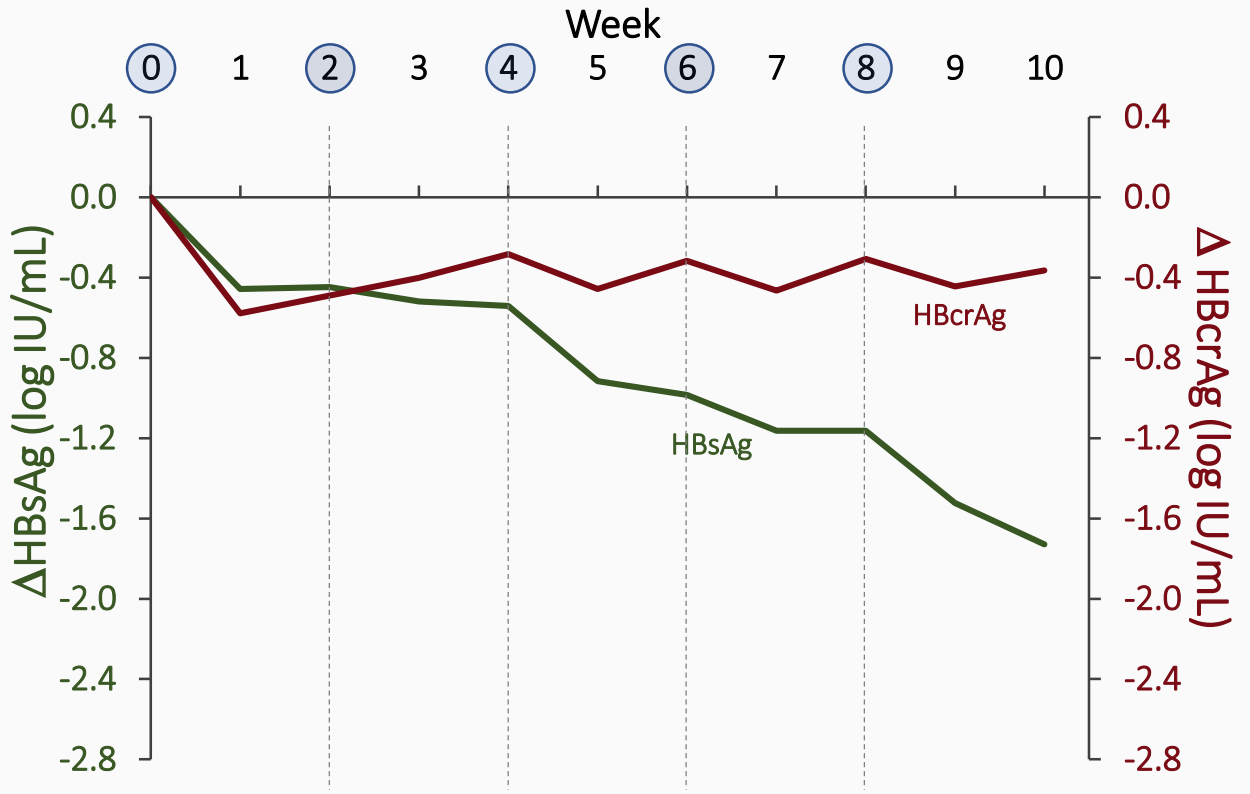
Mean Change from Baseline in HBcrAg

Dosing Day: All Groups Bi-weekly only (Cohort 4)

HBsAg and HBcrAg in HBeAg- Patients With the Largest Individual Declines (Cohort 4)



Patient With Largest Individual HBsAg Decline



Patient with Largest Individual HBcrAg Decline

Dosing Day

Overall Safety: Treatment-Emergent Adverse Events

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	
n (%)	HBeAg- 0.2 mg/kg Monthly n=6	HBeAg- 0.4 mg/kg Monthly n=6	HBeAg+ 0.4 mg/kg Monthly n=6	HBeAg- 0.4 mg/kg Bi-weekly n=12	Placebo n=6
Any AE *Drug-related*	5 (83) *3 (50)*	5 (83) *4 (67)*	2 (33) *2 (33)*	8 (67) *4 (42)*	5 (83) *2 (33)*
Grade 3–4 AEs	1 (17)	0	0	0	0
Serious AEs	1 (17)[a]	0	0	0	0
Discontinuation due to an AE	0	1 (17)[b]	0	1[c]	0
Grade 3–4 lab[d] abnormalities	4 (67)	5 (83)	4 (67)	9 (75)	4 (67)

[a]Left cochleovestibular deficit, not related to study treatment.

[b]Discontinued after the 2nd dose due to acute HEV super-infection and "HBV blip"(HBV-DNA 88 IU/mL)[1].

[c]Discontinued after the 3rd dose due to mild infusion reaction, arthralgia and hair loss.

[d]Isolated ↑ glucose, ↓ lymphocytes and ↓ phosphate in all groups including placebo.

- Most AEs to date have been mild and transient
- 17/18 (94%) subjects in Cohorts 1–3 received all three monthly doses
- 11/12 (92%) in Cohort 4 received all five bi-weekly doses

Streinu-Cercel A, *et al. J Hepatol* 2017;66(suppl 1):S688–S689.

Conclusions

- Treatment with ARB-1467 was generally well tolerated
- All subjects receiving ARB-1467 experienced a reduction in HBsAg from baseline
- Greater HBsAg reductions were observed with more frequent dosing (bi-weekly) and at the higher dose (0.4 mg/kg)

Conclusions

- Treatment with ARB-1467 was generally well tolerated
- All subjects receiving ARB-1467 experienced a reduction in HBsAg from baseline
- Greater HBsAg reductions were observed with more frequent dosing (bi-weekly) and at the higher dose (0.4 mg/kg)
- On treatment reductions in HBcrAg and HBV-RNA were observed in some individual patients
- Overall no apparent correlation was observed between declines in HBV-RNA or HBcrAg and declines in HBsAg
  - Data limited due to small sample size and short treatment duration
- Evaluation of the utility of these markers across different populations and treatment durations is required