Arbutus BIOPHARMA

Curing Chronic Hepatitis B

An RNAi for the Treatment Of Chronic Hepatitis B Infection: Clinical Update

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Chronic Hepatitis B Drug Development

HBV Presents a Significant Unmet Medical Need

>257M
people are chronically infected with HBV, globally.

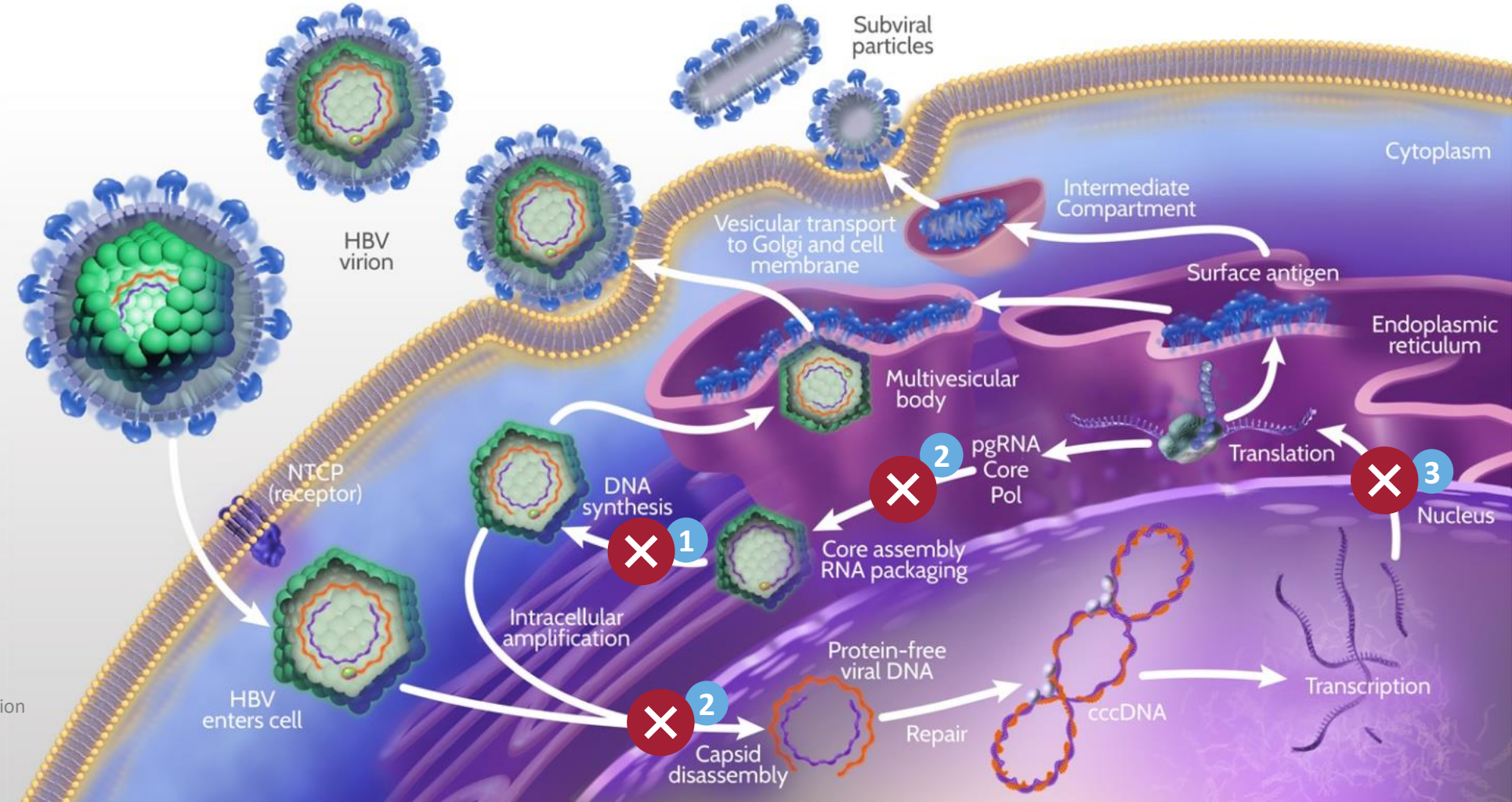
~900k
people die every year as a consequence despite the availability of effective vaccines and antivirals.

Sources: Global Hepatitis Report and Hepatitis B Fact Sheet, WHO (2017) http://www.who.int/mediacentre/factsheets/fs204/en/
Kowdley et al. Hepatology (2012) Prevalence of Chronic Hepatitis B Among Foreign-Born Persons Living in the US by Country of Origin

HBV Lifecycle Illustrates Key Points for Intervention

A combination of agents with complementary MOA **is needed to cure HBV**

1. **Nucleoside Analogue**
2. **Capsid Inhibitor**
3. **RNAi & RNA Destabilizer**



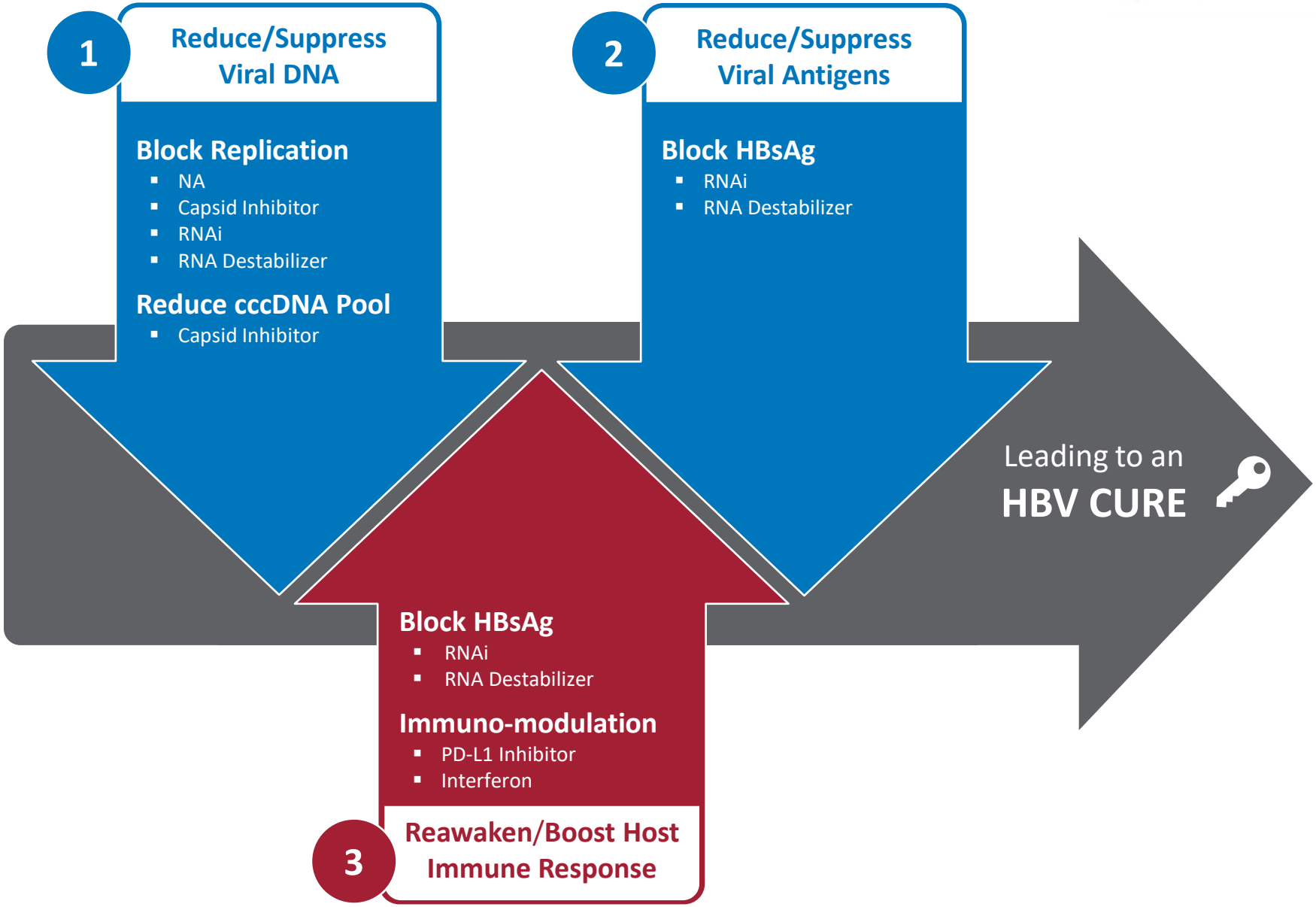
MOA: Mechanism of Action

Keys to Therapeutic Success

Suppress HBV DNA and viral antigens

Reawaken host immune response

Therapeutic success will **require a combination of agents** with complementary MOAs

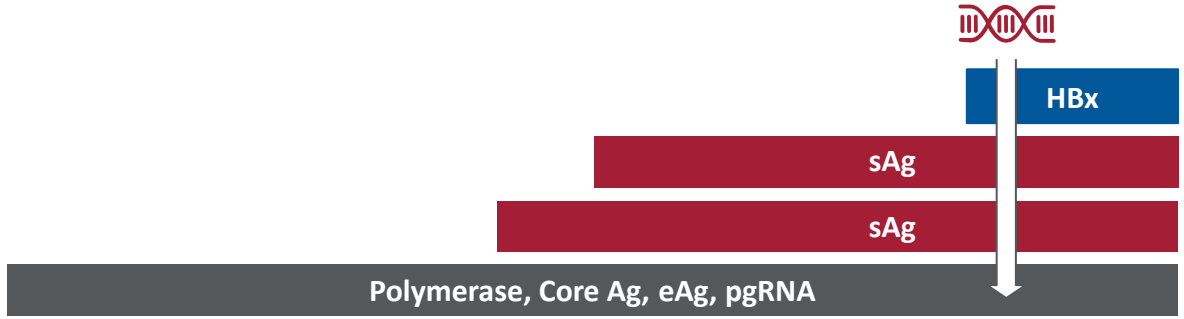


MOA: Mechanism of Action | **NA:** Nucleoside Analogue | **HBsAg**: HBV Surface Antigen

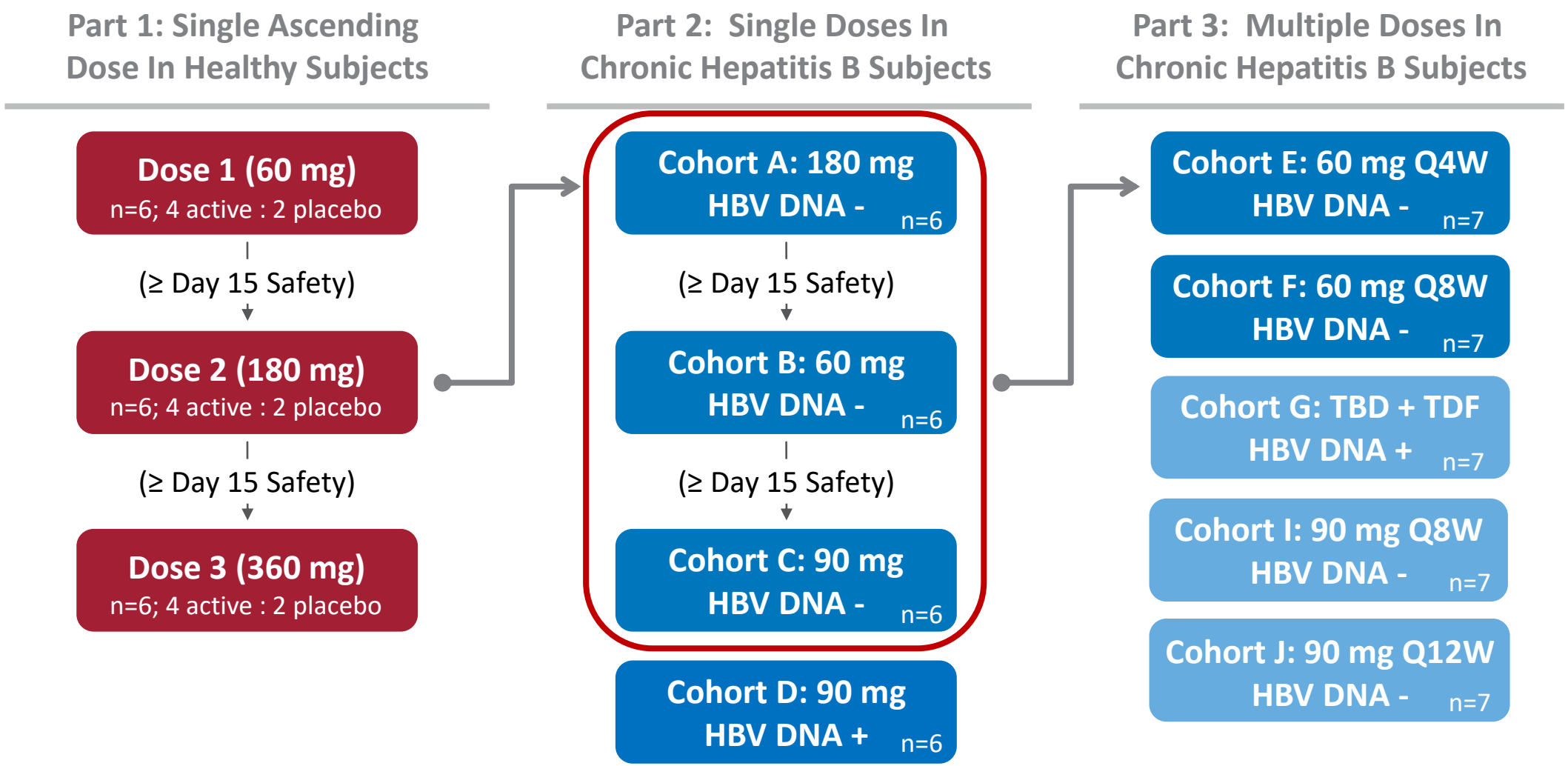
AB-729
RNAi Therapeutic

Proprietary GalNAc-conjugate delivery technology provides liver targeting and enables **subcutaneous dosing**

- Single trigger RNAi agent targeting all HBV transcripts
- Inhibits HBV replication and lowers all HBV antigens
- Pan-genotypic activity across HBV genotypes
- Demonstrated complementarity with capsid inhibitors
- Actively targets the liver
- Active against cccDNA derived and integrated HBsAg transcripts
- Clean profile in long term preclinical safety studies



AB-729-001 Study



Key Inclusion Criteria

- Cohorts A#, B#, C#, D*, E# and F#
  - Age 18 – 65 years old
  - #At least 6 months of stable nucleos(t)ide analogue (NA) therapy (ETV, TDF, TAF) prior to Screening
  - HBeAg positive or negative
  - #HBV-DNA < LLOQ and HBsAg ≥ 250 IU/mL at Screening
  - *HBV-DNA ≥ 1,000 IU/mL and HBsAg ≥ 250 IU/mL at Screening
  - Non-cirrhotic, Fibroscan® result of ≤10 kPa
  - ALT/AST at Screening:
    - Part 2 (Cohorts A, B, C and D): ≤ 5x ULN
    - Part 3 (Cohort E and F): ≤ 2x ULN

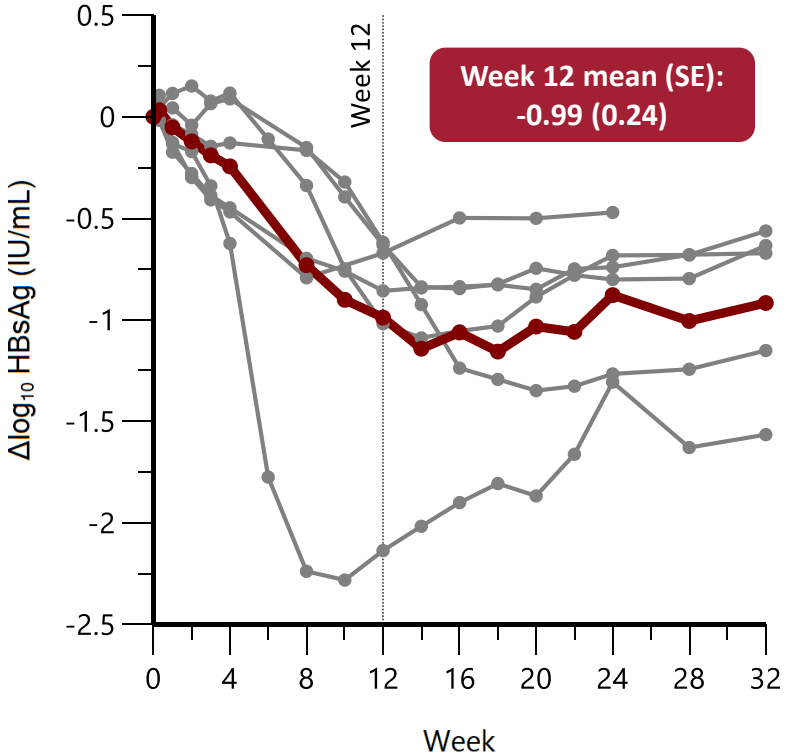
Baseline Characteristics

Baseline Measure	Cohort A 180 mg (N=4)	Cohort B 60 mg (N=6)	Cohort C 90 mg (N=6)	Cohort D HBV DNA+ 90 mg (N=5*)	Cohort E 60 mg Q4W (N=7)	Cohort F 60 mg Q8W (N=7)
Age in years, mean (range)	42.8 (35-53)	48.2 (33-56)	54.8 (47-62)	43.6 (35-57)	45.1 (33-63)	44.0 (31-59
Male gender, n (%)	3 (75%)	3 (50%)	6 (100%)	3 (60%)	4 (57%)	4 (57%)
BMI, mean (SD)	23.7 (3.62)	26.6 (3.23)	25.2 (1.96)	29.2 (5.42)	27.7 (5.01)	23.7 (2.17)
Race, n (%)						
Asian	0	3 (50%)	6 (100%)	0	1 (14%)	5 (71%)
White	4 (100%)	3 (50%)	0	4 (80%)	6 (86%)	1 (14%)
Pacific Islander	0	0	0	1 (20%)	0	1 (14%)
ALT (U/L), mean (SD)	39.3 (35.36)	20.0 (6.52)	25.5 (9.23)	31.6 (13.43)	22.4 (10.52)	23.4 (15.2)
HBV eAg negative, n (%)	3 (75%)	6 (100%)	6 (100%)	5 (100)	7 (100%)	6 (86%)
HBsAg (IU/mL), mean (range)	8577 (4720 – 10289)	2095 (405 – 5110)	822 (261 – 1400)	2336 (317 – 6451)	5372 (584 – 11761)	5354 (667-18605)
HBV DNA (IU/mL), mean (range)	N/A	N/A	N/A	86840 (1220 – 360560)	N/A	N/A

*One subject experienced a spontaneous HBV flare prior to dosing and was excluded from the analysis

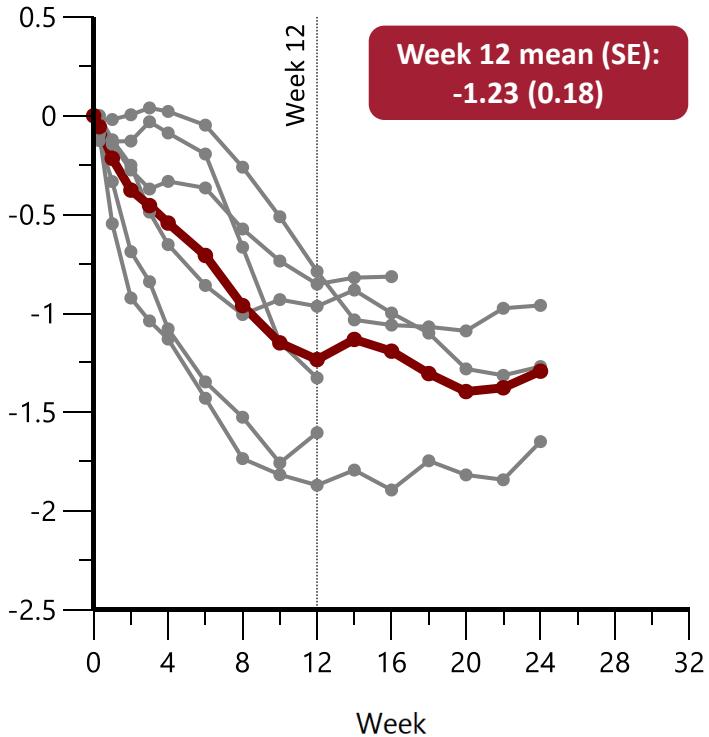
Single Doses of AB-729 Result in Comparable Mean HBsAg Declines at Week 12 Followed by a Sustained Plateau Phase

AB-729 60 mg single dose (N=6)*



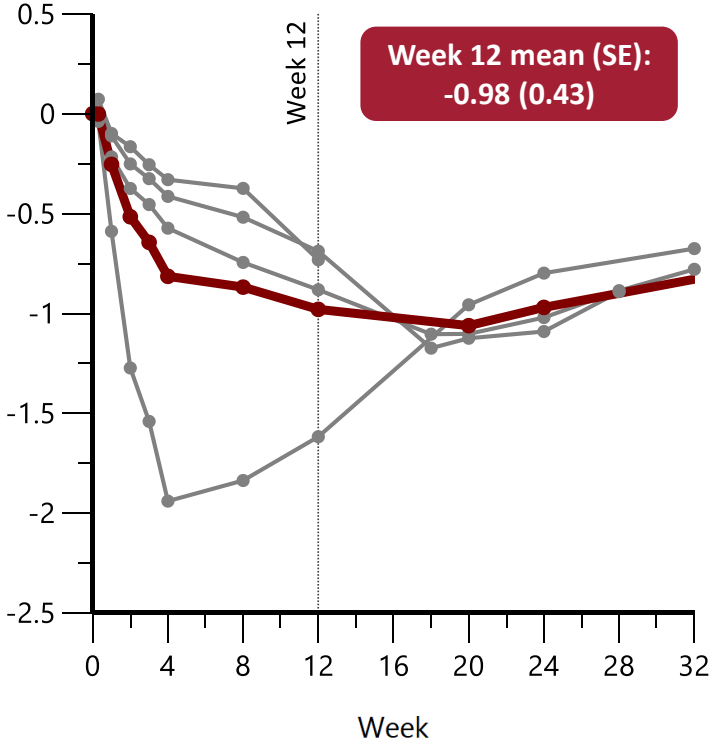
3/6 HBsAg <100 IU/mL
1/6 HBsAg <10 IU/mL

AB-729 90 mg single dose (N=6)**



5/6 HBsAg <100 IU/mL
1/6 HBsAg <10 IU/mL

AB-729 180 mg single dose (N=4)#



0/4 HBsAg <100 IU/mL

mean
individual

*N=5 at Week 10, 14, 18, 22, 28, and 32
**N=4 at Week 14 and 16; N=3 at Weeks 18 – 24
#N=3 after Week 12; nominal visits ± 7 days

AB-729 was safe and well tolerated after single doses

- No SAEs or discontinuations due to AEs
- No treatment-related Grade 3 or 4 AEs or laboratory abnormalities
  - 1 subject (Cohort A) with rapid decline in HBsAg of ~2.0 log_{10} IU/mL had an unrelated Gr 2 AE of food poisoning resulting in unrelated transient Grade 3 AEs of ALT/AST elevation (without bilirubin changes)
- Injection site TEAEs were mild (erythema, pain, pruritis, bruising) or moderate (pain) and transient
- No clinically meaningful changes in ECGs or vital signs

Subjects, n (%)	Cohort A (180 mg) N=4	Cohort B (60 mg) N=6	Cohort C (90 mg) N=6
Subjects with any TEAE	4 (100)	4 (67)	5 (83)
Subjects with related TEAEs	3 (75)	2 (33)	5 (83)
Grade 1	1 (25)	2 (33)	2 (33)
Grade 2	2 (50)	0	3 (50)
Grade 3	0	0	0
Grade 4	0	0	0
Most common related TEAEs (in ≥ 2 subjects):			
Injection site pain	0	0	5 (83)†
Injection site erythema	0	1 (17)	0
ALT elevation	2 (50)	0	0
AST elevation	1 (25)	0	0
Headache	2 (50)	0	0

Grading criteria based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1., July, 2017

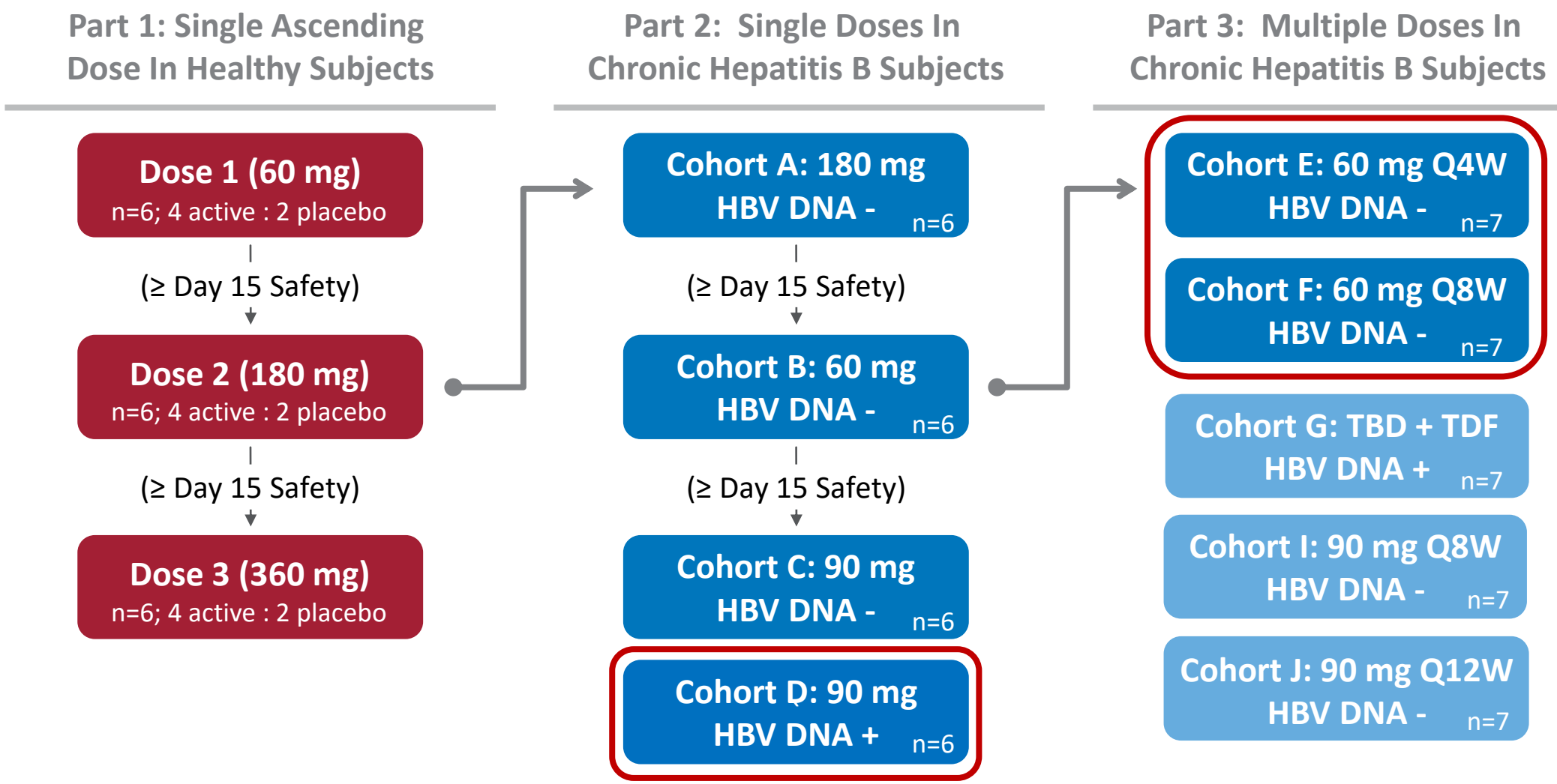
ALT and AST elevations were all Grade 1 excepting one Grade 2 ALT, all were asymptomatic without bilirubin changes

† 4/5 subjects from same site; 2 Gr 2 TEAEs had AB-729 dose erroneously split into 2 injections, all TEAEs lasted <1 hour

‡ n, % is number of events out of 54 total AB-729 doses administered

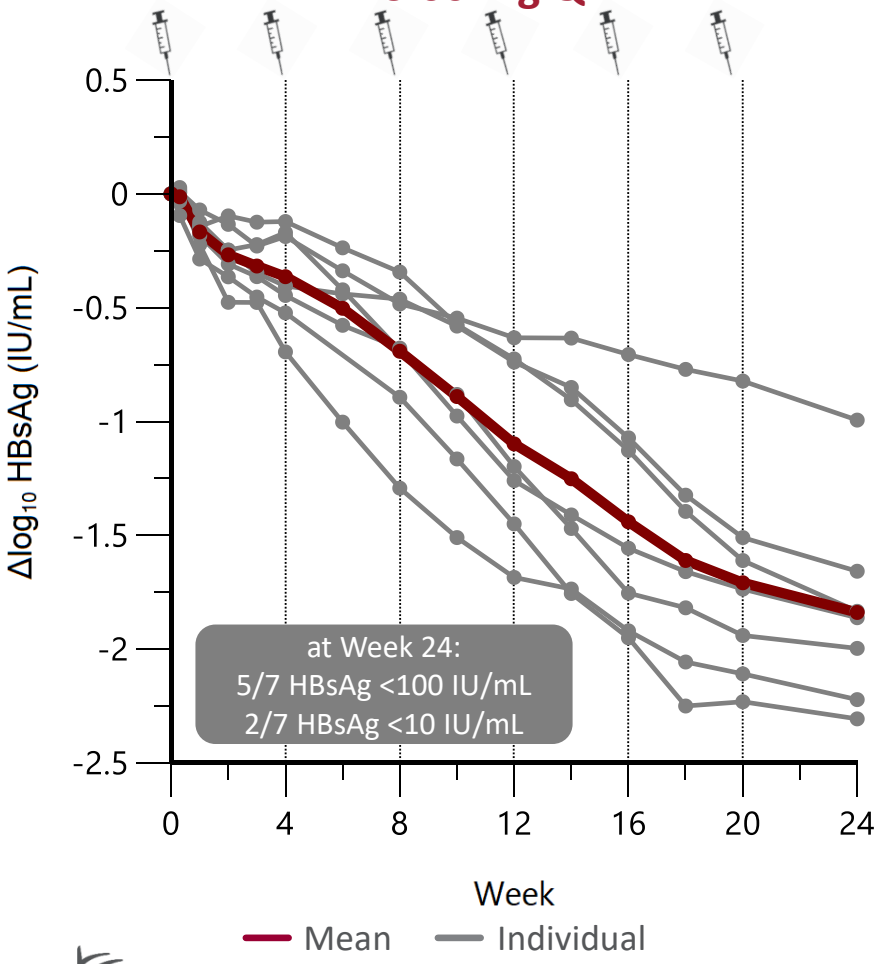
MF Yuen, et at. AASLD 2020

AB-729-001 Study



Repeat Dosing of AB-729 60 mg Every 8 Weeks Results in Comparable Mean HBsAg Declines to 60 mg Every 4 Weeks at Week 16

AB-729 60 mg Q4W



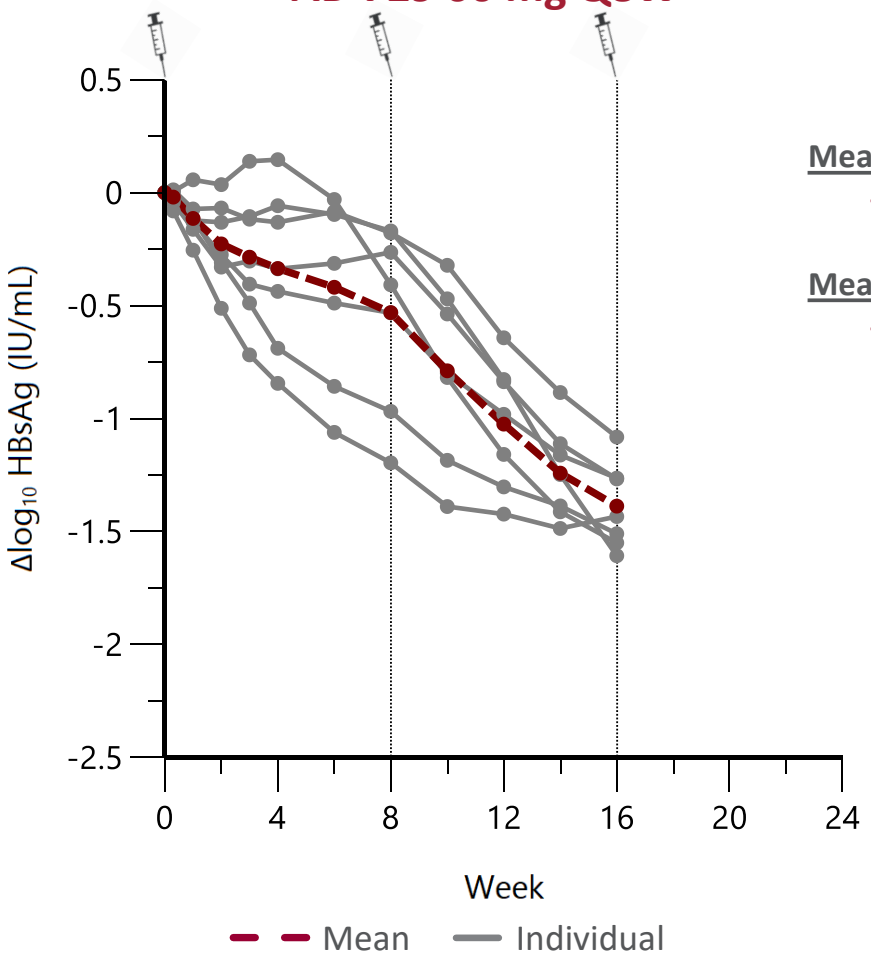
Mean (SE) Week 12:
-1.10 (0.15)

Mean (SE) Week 16:
-1.44 (0.18)

Mean (SE) Week 20:
-1.71 (0.18)

Mean (SE) Week 24:
-1.84 (0.16)

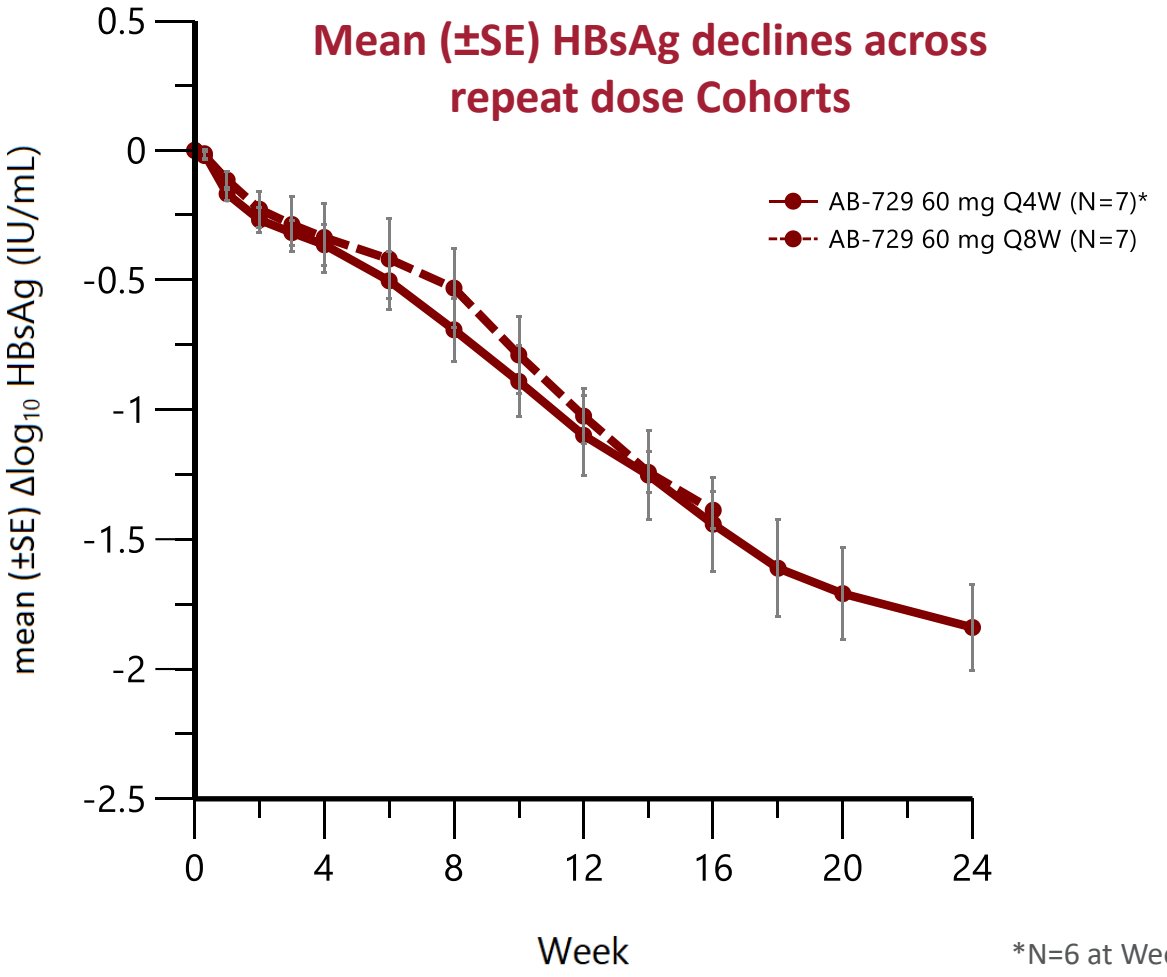
AB-729 60 mg Q8W



Mean (SE) Week 12:
-1.02 (0.11)

Mean (SE) Week 16:
-1.39 (0.07)

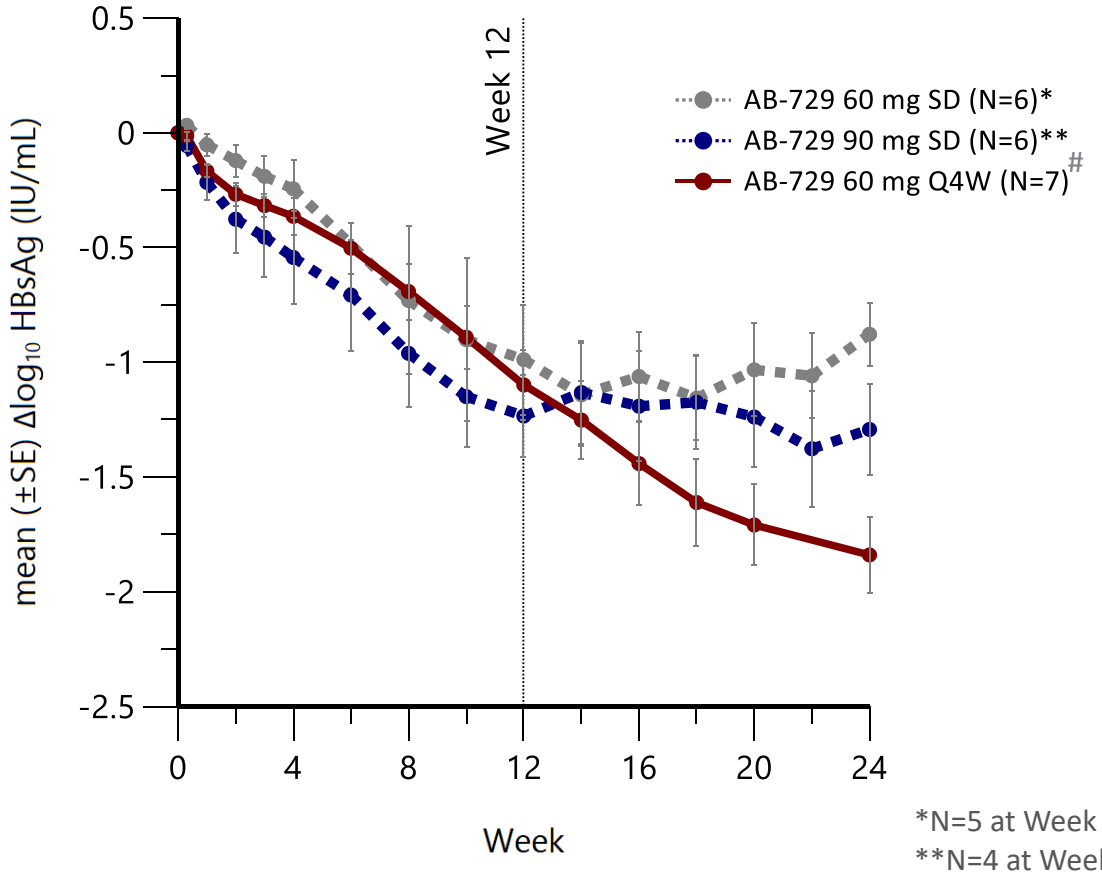
Repeat Dosing of AB-729 60 mg Every 8 Weeks Results in Comparable Mean HBsAg Declines to 60 mg Every 4 Weeks at Week 16



*N=6 at Week 6
Q4W: every 4 weeks; Q8W: every 8 weeks

Repeat Dosing of AB-729 60 mg Every 4 Weeks Results in Continuous Mean HBsAg Declines Beyond Week 12

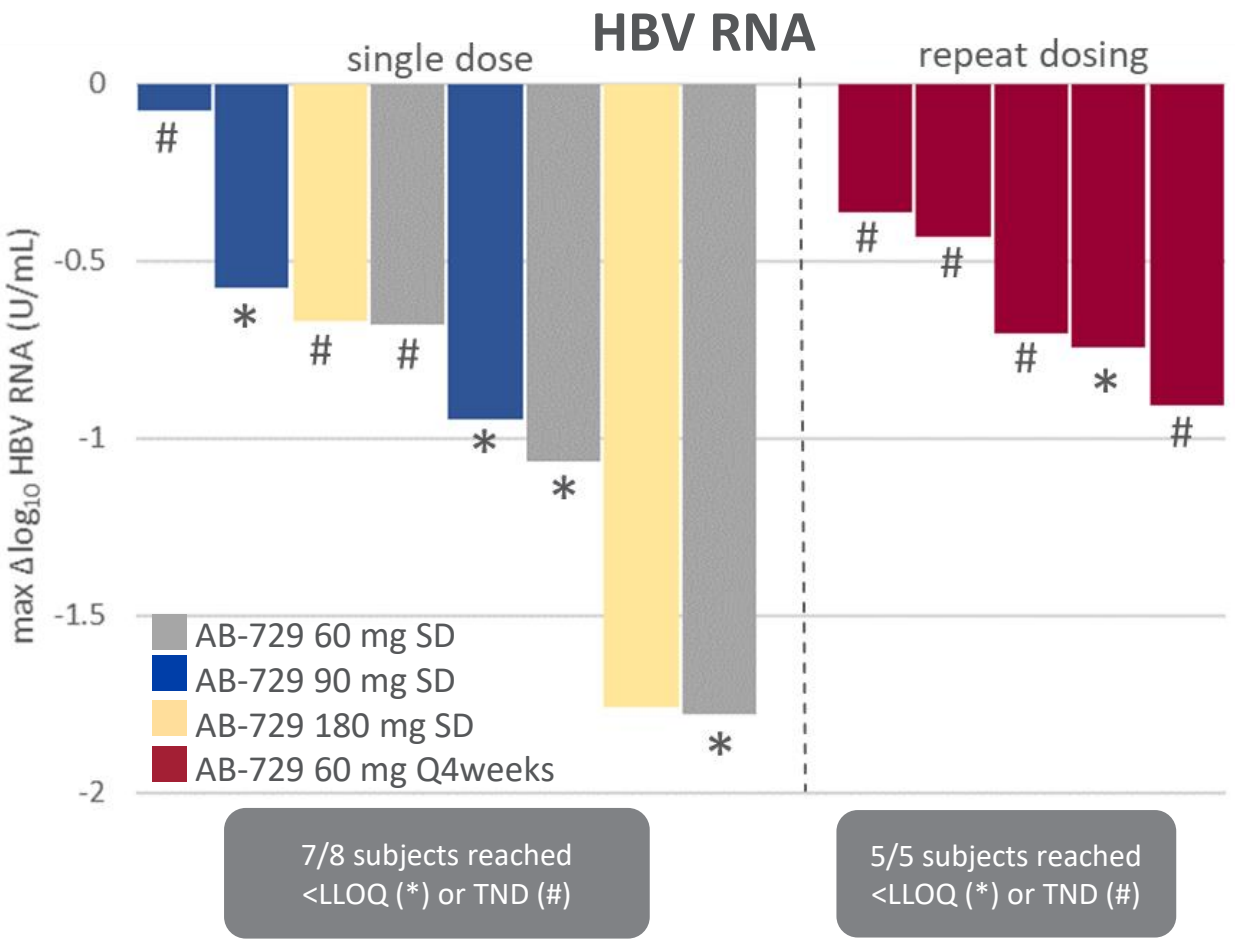
Mean (±SE) HBsAg declines across single and repeat dose Cohorts

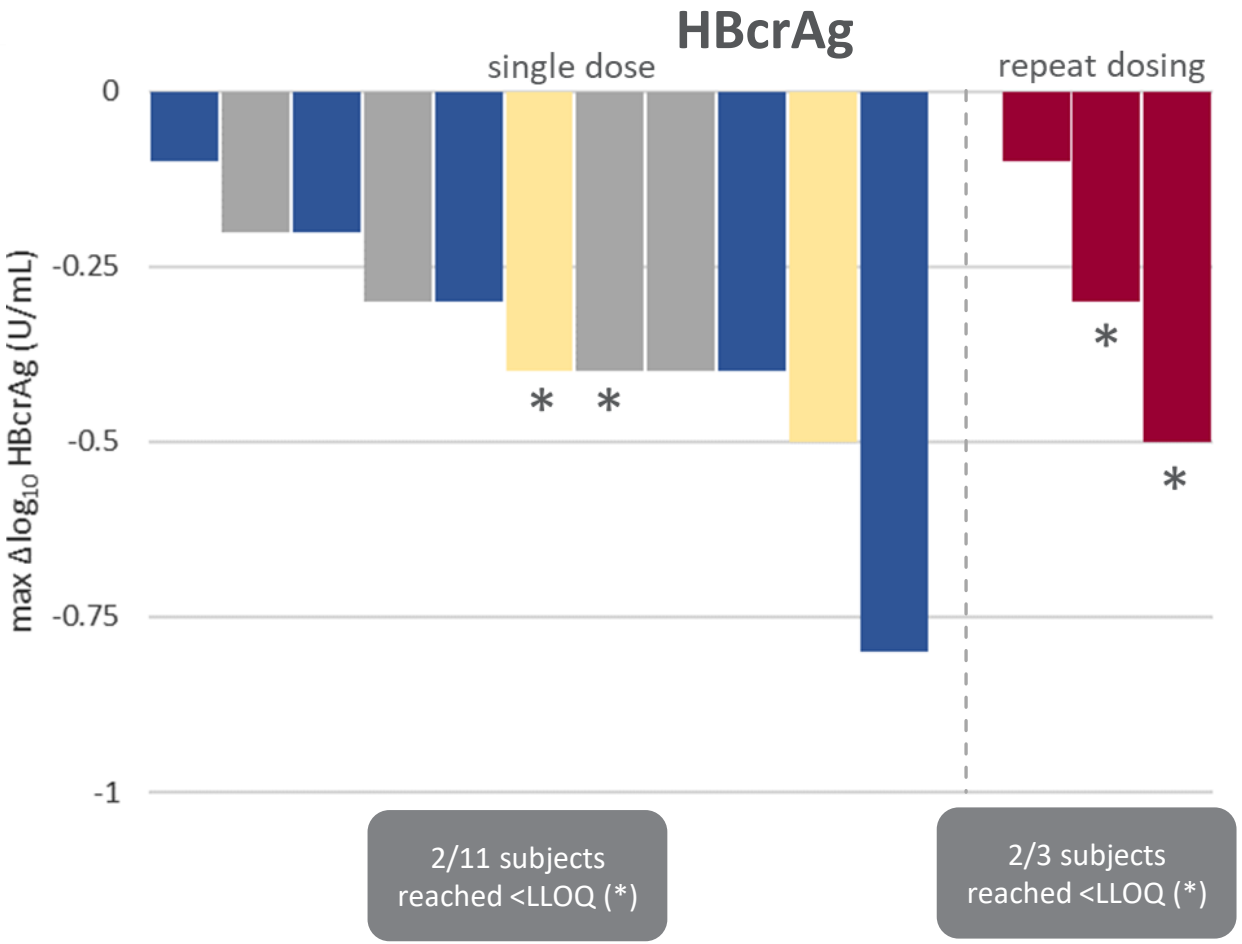


*N=5 at Week 10, 14, 18 and 22
**N=4 at Week 14 - 20; N=3 at Weeks 22 – 24
#N=6 at Week 6
SD: single dose; Q4W: every 4 weeks

AB-729 reduces HBV RNA to the limits of quantification or detection in most subjects; HBcrAg also declines

Maximum reductions shown through Week 12 in subjects with quantifiable data at baseline



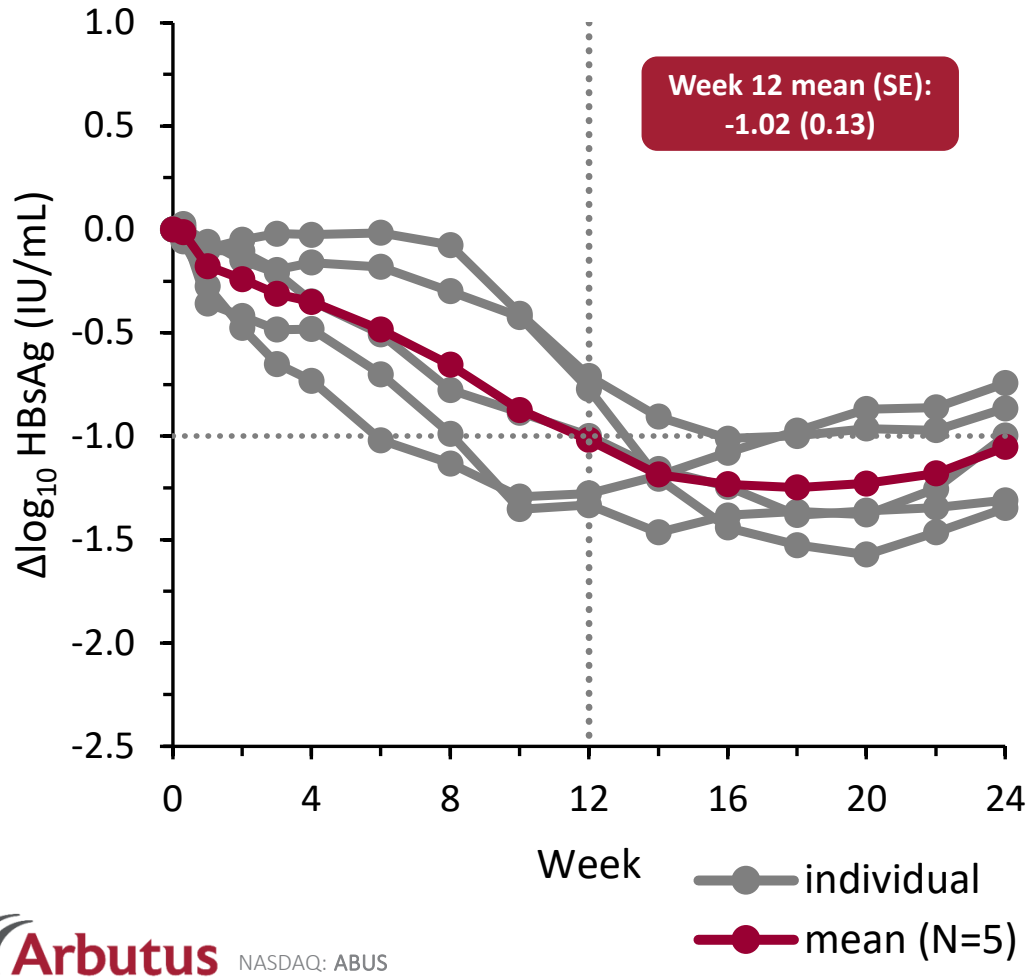


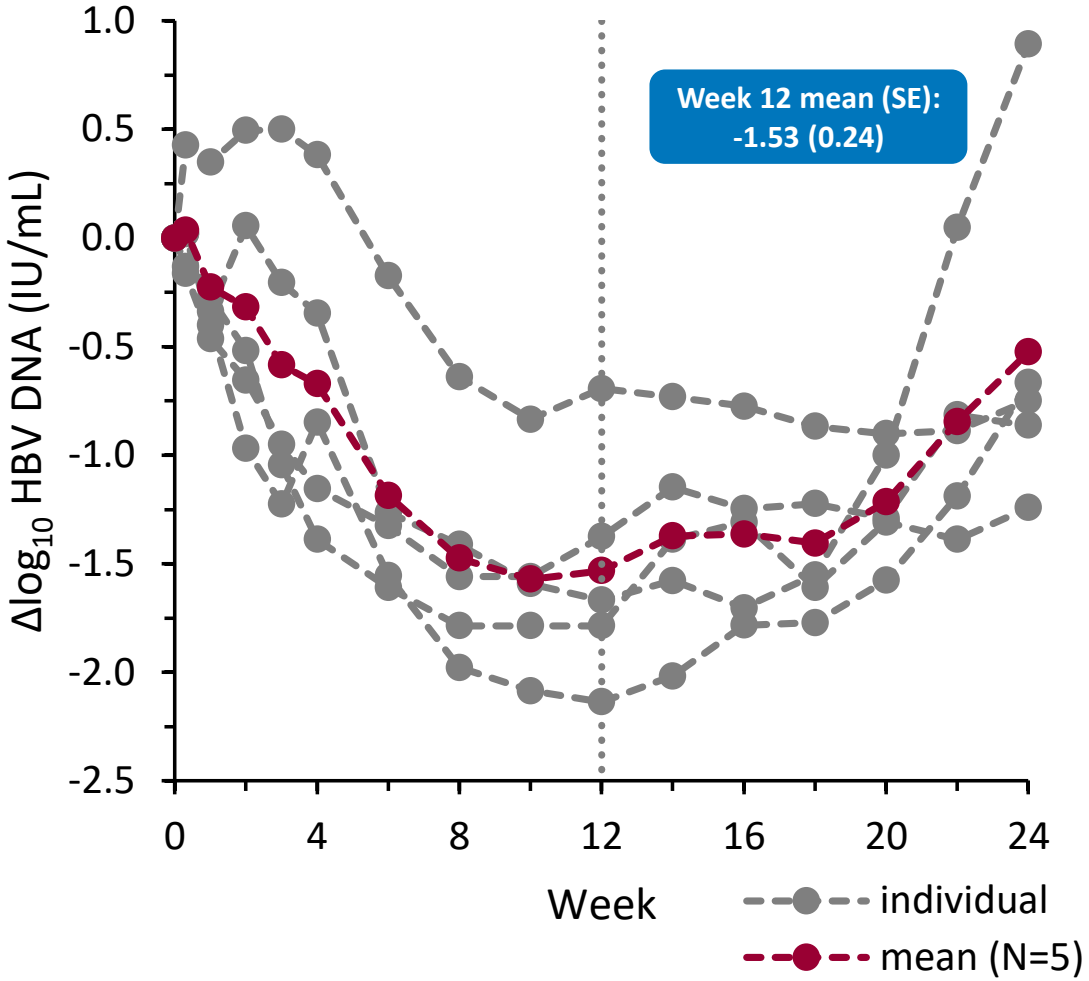
LLOQ = lower limit of quantitation; TND = target not detected; SD = single dose
HBcrAg samples <LLOQ (3.0 $\log_{10}$ IU/mL) assigned a value of 2.9 $\log_{10}$ IU/mL
HBV RNA samples <LLOQ (1.65 $\log_{10}$ IU/mL) or target not detected assigned a value of 1.64 $\log_{10}$ IU/mL

MF Yuen, et at. AASLD 2020

AB-729 90 mg Single Dose Reduces HBsAg and HBV DNA in HBV DNA Positive CHB subjects

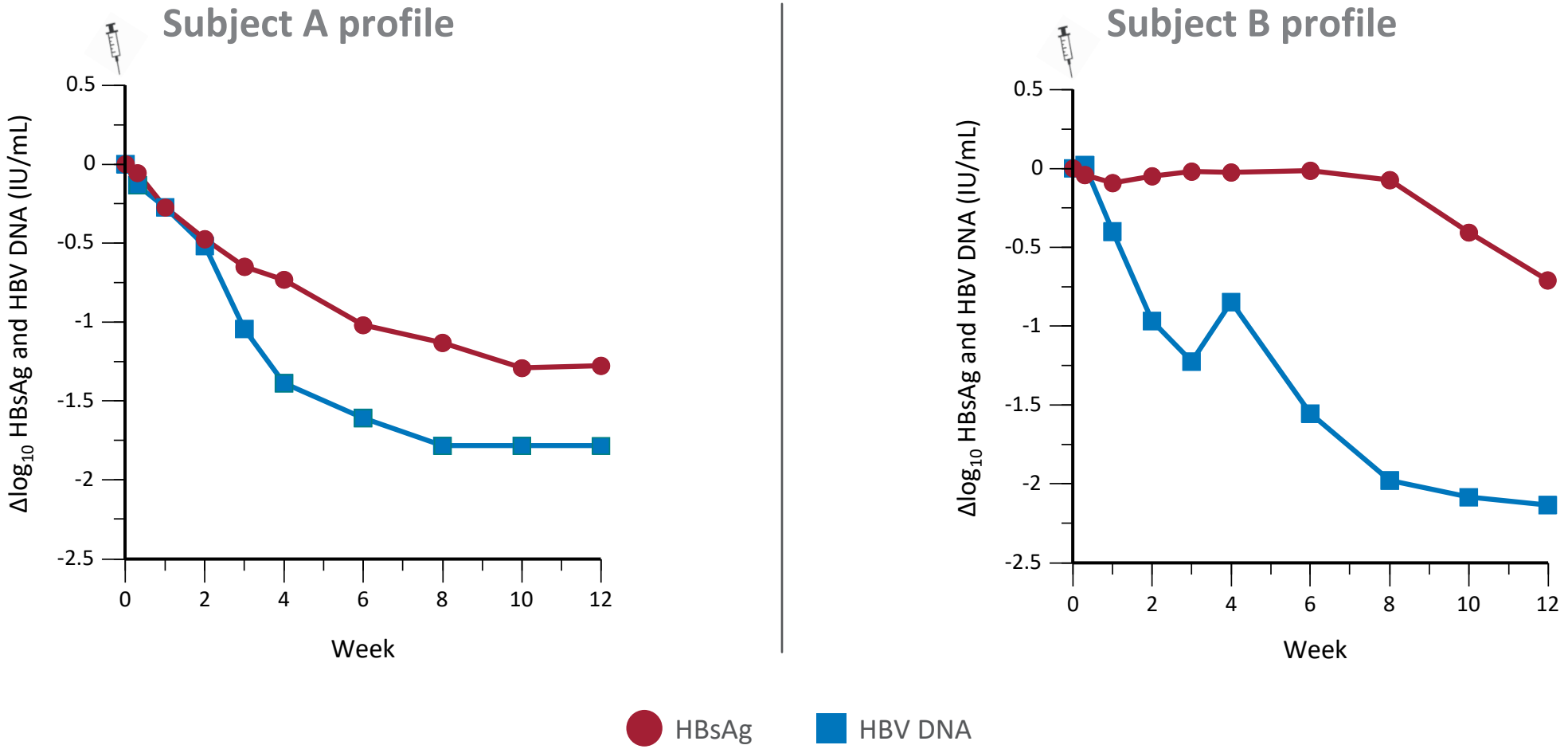
These data continue to support dosing intervals of up to 12 weeks



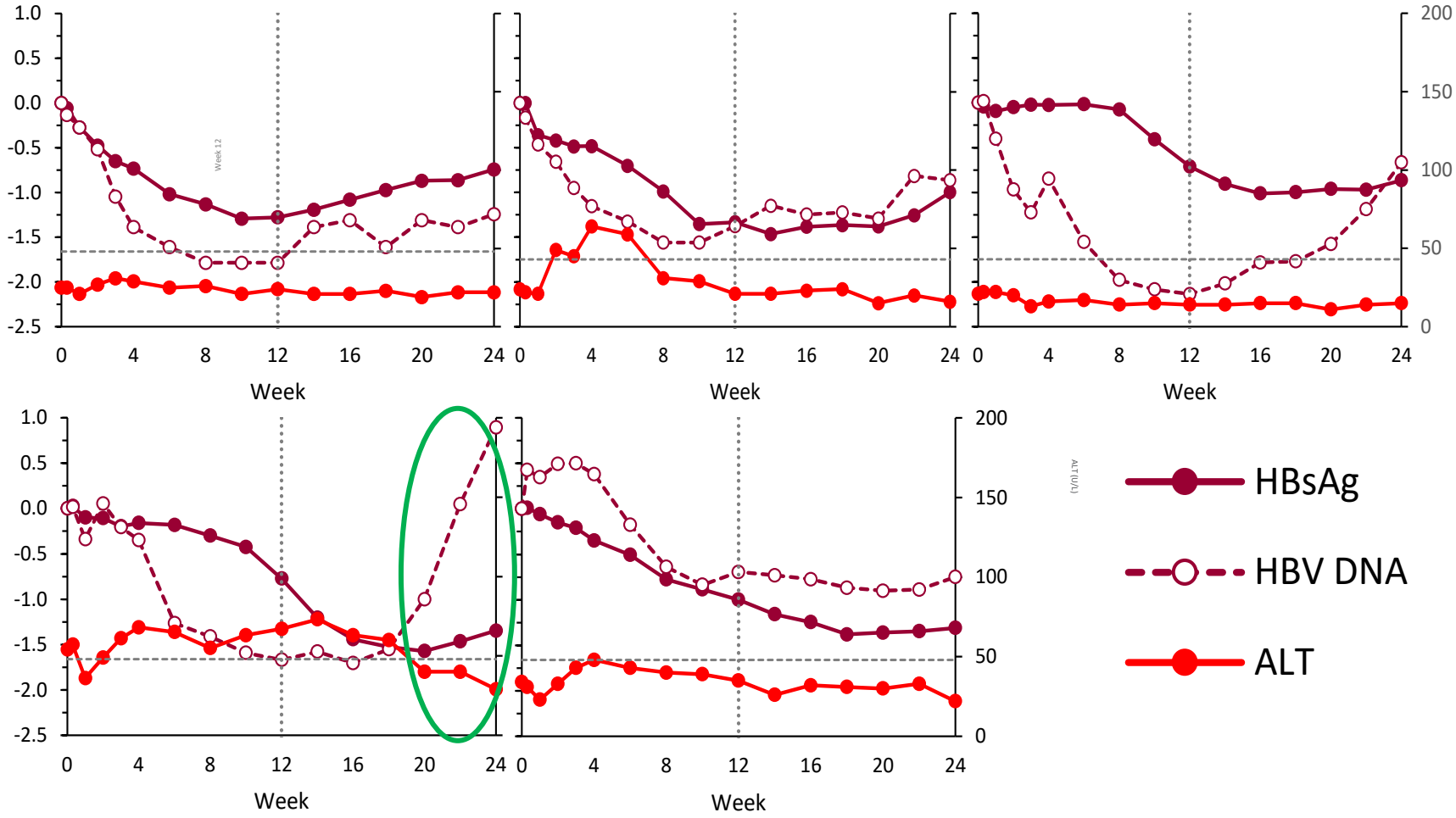


E. Gane, et at. APASL 2021

Different response profiles following a single dose of AB-729 90 mg in HBV DNA positive CHB subjects



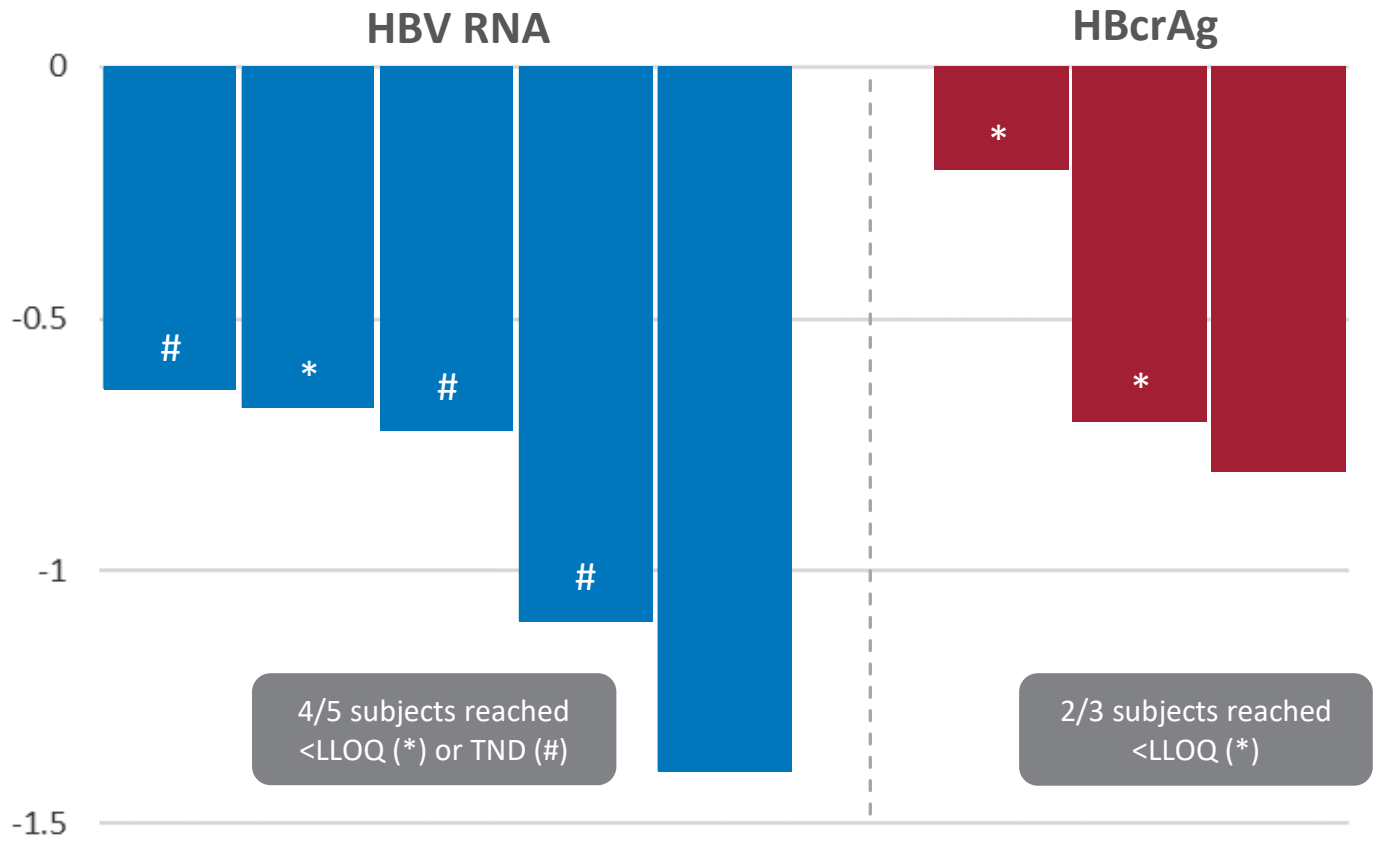
Individual profiles following a single dose of AB-729 90 mg in HBV DNA positive CHB subjects: No evidence of ALT elevations despite increases in HBV DNA



*dotted horizontal line represents ALT ULN (43 U/L for females, 48 U/L for males)

AB-729 reduces HBV RNA and HBcrAg to the limits of quantification or detection in most HBV DNA+ subjects

Maximum reductions shown up to Week 12 in subjects with quantifiable data at baseline



LLOQ = lower limit of quantitation; TND = target not detected; SD = single dose
HBcrAg samples <LLOQ (3.0 log10 IU/mL) assigned a value of 2.9 log10 IU/mL
HBV RNA samples <LLOQ (1.65 log10 IU/mL) or target not detected assigned a value of 1.64 log10 IU/mL

E. Gane, et at. APASL 2021

AB-729 was safe and well tolerated after single and multiple doses

- No SAEs or discontinuations due to AEs
- No treatment-related Grade 3 or 4 AEs or laboratory abnormalities
- Injection site TEAEs were mild (erythema, pain, pruritis, bruising) or moderate (pain) and transient
- No clinically meaningful changes in ECGs or vital signs

Subjects, n (%)	Cohort D (90 mg SD HBV DNA+) [N=5]	Cohort E (60 mg Q4W) [N=7]	Cohort F (60 mg Q8W) [N=7]	TOTAL [N=19]
Subjects with any TEAE	3 (60)	4 (57)	4 (57)	11 (58)
Subjects with related TEAEs (all Grade 1)	1 (20)	2 (29)	4 (57)	7 (37)
Most common related TEAEs (in ≥ 2 subjects):				
Injection site pain	0	0	2 (29)	2 (3)[#]
Injection site erythema	0	2 (29)	1 (14)	4 (6)[#]
Injection site bruising	1 (20)	2 (29)	0	3 (4)[#]
Laboratory Abnormalities (in ≥ 2 subjects):				
ALT elevation				
Grade 1	2 (40)	2 (29)	1 (14)	5 (26)
Grade 2[‡]	0	2 (29)	1 (14)[†]	3 (16)
AST elevation (Gr 1)	0	2 (29)	2 (29)	4 (21)
Sodium (low, Gr 1)	0	1 (14)	1 (14)	2 (11)

TEAE: treatment-emergent adverse event
Grading criteria based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1
[#]n, % is number of events out of 70 total AB-729 doses administered
‡Grade 2 ALT elevations were transient and all improved to Grade 1
†Subject had history of pre-study Grade 1 ALT abnormalities

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AB-729 Clinical Summary

Repeat 60 mg Q4W dosing with AB-729 resulted in a continuous and robust mean HBsAg decline at week 24 (-1.84 log10 IU/mL, N=7)

Repeat dosing of AB-729 60 mg every 8 weeks results in comparable mean HBsAg declines relative to 60 mg every 4 weeks at week 16 (-1.44 log10 IU/mL vs -1.37 log10 IU/mL, $p<0.7$)

In HBV DNA positive CHB subjects, a single 90 mg AB-729 dose resulted in robust mean HBsAg (-1.02 log10 IU/mL) and HBV DNA (-1.53 log10 IU/mL) declines at week 12, as well as decreases in HBV RNA and core-related antigen

- Similar mean HBsAg reductions were observed in HBV DNA positive and negative CHB subjects
- These findings support complete target engagement by AB-729

AB-729 remains generally safe and well tolerated

These results support advancing AB-729 to Phase 2 combination studies with AB-729 dosing as infrequently as every 8 or 12 weeks

Thank you!