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*Curing Chronic Hepatitis B*

# Repeat dosing of the GalNAc-siRNA AB-729 in subjects with chronic hepatitis B results in robust and sustained HBsAg suppression

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- Chief of Division of Gastroenterology and Hepatology, Department of Medicine, The University of Hong Kong, Hong Kong
- A therapeutic expert and pioneering clinical researcher leading numerous studies on novel antiviral and immunomodulatory agents for the treatment of chronic hepatitis B virus infection
- Research includes prevention, natural history, virology, treatment of chronic hepatitis B and C and is actively involved with cutting-edge research on novel markers for hepatitis B infection and occult hepatitis B infection
- One of the top international researchers in the field of hepatitis B, with more than 470 papers published in world-renowned medical journals

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# Disclosures

MFY acted as a consultant for AbbVie, Assembly Biosciences, Aligos Therapeutics, Arbutus Biopharma, Bristol Myer Squibb, Clear B Therapeutics, Dicerna Pharmaceuticals, Finch Therapeutics, GlaxoSmithKline, Gilead Sciences, Immunocore, Janssen, Merck Sharp and Dohme, Hoffmann-La Roche and Springbank Pharmaceuticals, Vir Biotechnology and receives grant/research support from Assembly Biosciences, Aligos Therapeutics, Arrowhead Pharmaceuticals, Bristol Myer Squibb, Fujirebio Incorporation, Gilead Sciences, Immunocore, Merck Sharp and Dohme, Hoffmann-La Roche, Springbank Pharmaceuticals and Sysmex Corporation.

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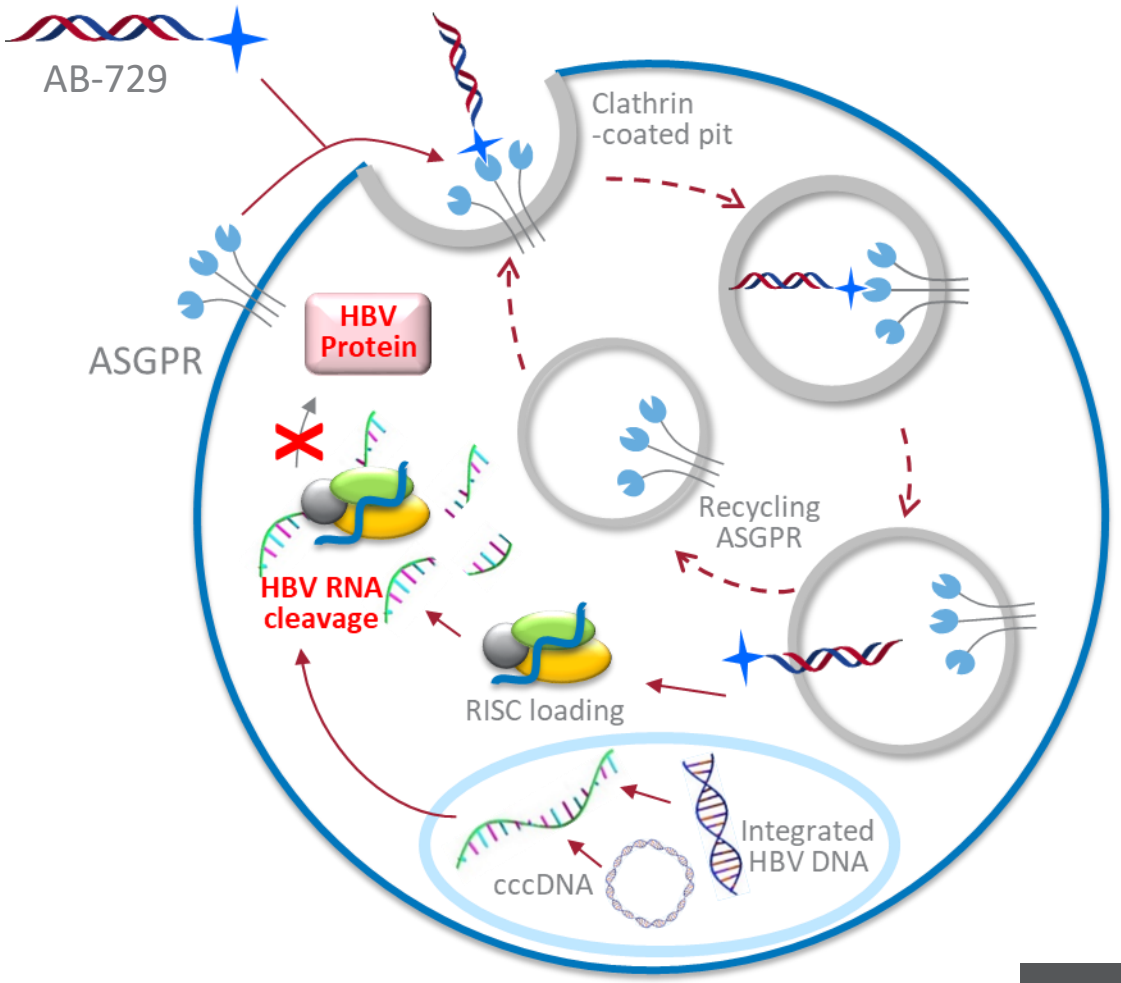
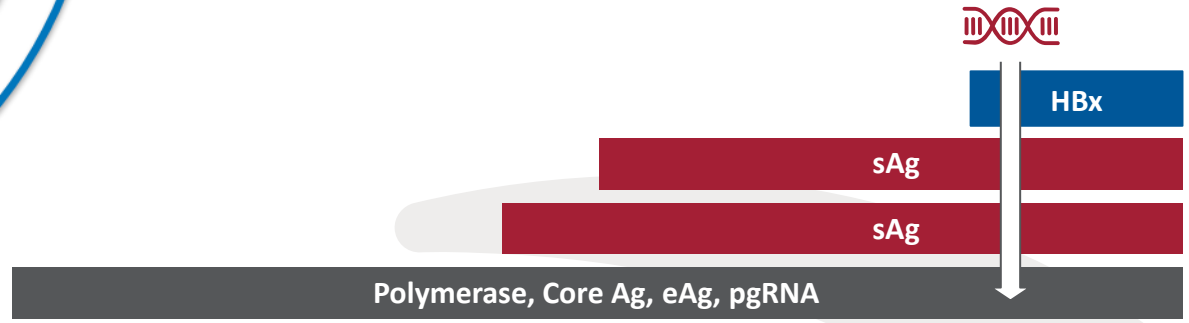
# AB-729 GalNAc-siRNA Therapeutic




- Single trigger RNA interference agent administered subcutaneously
- Proprietary liver targeting technology based on GalNAc ligand interaction with ASGPr
- Inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens
- Pan-genotypic activity across HBV genotypes

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# AB-729-001 Study Overview

*presentation includes data available through 01-Jun-2021*

## Part 1: Single Ascending Dose in Healthy Subjects

Dose 1 (60 mg)
n=6; 4 active : 2 placebo

(≥ Day 15 Safety)

Dose 2 (180 mg)
n=6; 4 active : 2 placebo

(≥ Day 15 Safety)

Dose 3 (360 mg)
n=6; 4 active : 2 placebo

## Part 2: Single Doses in Chronic Hepatitis B Subjects (open-label)

Cohort A: 180 mg HBV DNA - n=4

(≥ Day 15 Safety)

Cohort B: 60 mg HBV DNA - n=6

(≥ Day 15 Safety)

Cohort C: 90 mg HBV DNA - n=6

Cohort D: 90 mg HBV DNA + n=5

## Part 3: Repeat Doses in Chronic Hepatitis B Subjects (open-label)

Cohort E: 60 mg Q4W HBV DNA - n=7

Cohort F: 60 mg Q8W HBV DNA - n=7

Cohort G: 90 mg Q8W + TDF: HBV DNA + n=7

Cohort I: 90 mg Q8W HBV DNA - n=6

Cohort J: 90 mg Q12W HBV DNA - n=7

Cohort K: 90 mg Q8W HBV DNA -, HBeAg+ n=7

**Initially, AB-729 was dosed for 6 months.**

**An optional 6 month treatment extension was amended to the protocol, with 48 weeks of follow-up.**

HBV: Hepatitis B Virus | Q4W: every 4 weeks | Q8W: every 8 weeks | Q12W: every 12 weeks | TDF: tenofovir disoproxil fumarate

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# Key Inclusion Criteria

- **Cohorts E, F and I**
  - 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
  - Non-cirrhotic, Fibroscan® result of ≤10 kPa
  - ALT/AST ≤2x ULN at Screening

ETV: entecavir | TDF: tenofovir disoproxil fumarate | TAF: tenofovir alafenamide | ULN: upper limit of normal

# Baseline Characteristics

| Baseline Measure | Cohort E<br>AB-729 60 mg Q4W*<br>(N=7) | Cohort F<br>AB-729 60 mg Q8W<br>(N=7) | Cohort I<br>AB-729 90 mg Q8W<br>(N=6) |
|---|---|---|---|
| Age in years, mean (range) | 45.1 (33 – 63) | 44.0 (31 – 59) | 45.7 (38 – 54) |
| Male gender, n (%) | 4 (57%) | 4 (57%) | 4 (67%) |
| BMI, mean (SD) | 27.7 (5.01) | 23.7 (2.17) | 25.5 (3.11) |
| Race, n (%) | | | |
| Asian | 1 (14%) | 5 (71%) | 5 (83%) |
| Black | 0 | 1 (14%) | 0 |
| White | 6 (86%) | 1 (14%) | 1 (14%) |
| ALT (U/L), mean (SD) | 22.4 (10.52) | 23.4 (15.22) | 26.0 (10.20) |
| HBV eAg negative, n (%) | 7 (100%) | 6 (71%)** | 5 (83%) |
| HBsAg (IU/mL), mean (range) | 5,372 (584 – 11,761) | 5,354 (667 – 18,605) | 4,691 (338 – 19,017) |

*subjects switched to AB-729 60 mg Q12W after the Week 20 dose

** 1 subject counted as HBeAg negative was identified as “HBeAg borderline” (baseline HBeAg = 0.18 IU/mL, LLOQ = 0.11 IU/mL)

- All subjects were virologically suppressed on an NA (ETV, TDF or TAF) with HBV DNA < LLOQ (20 IU/mL)
- HBV genotype was not determined

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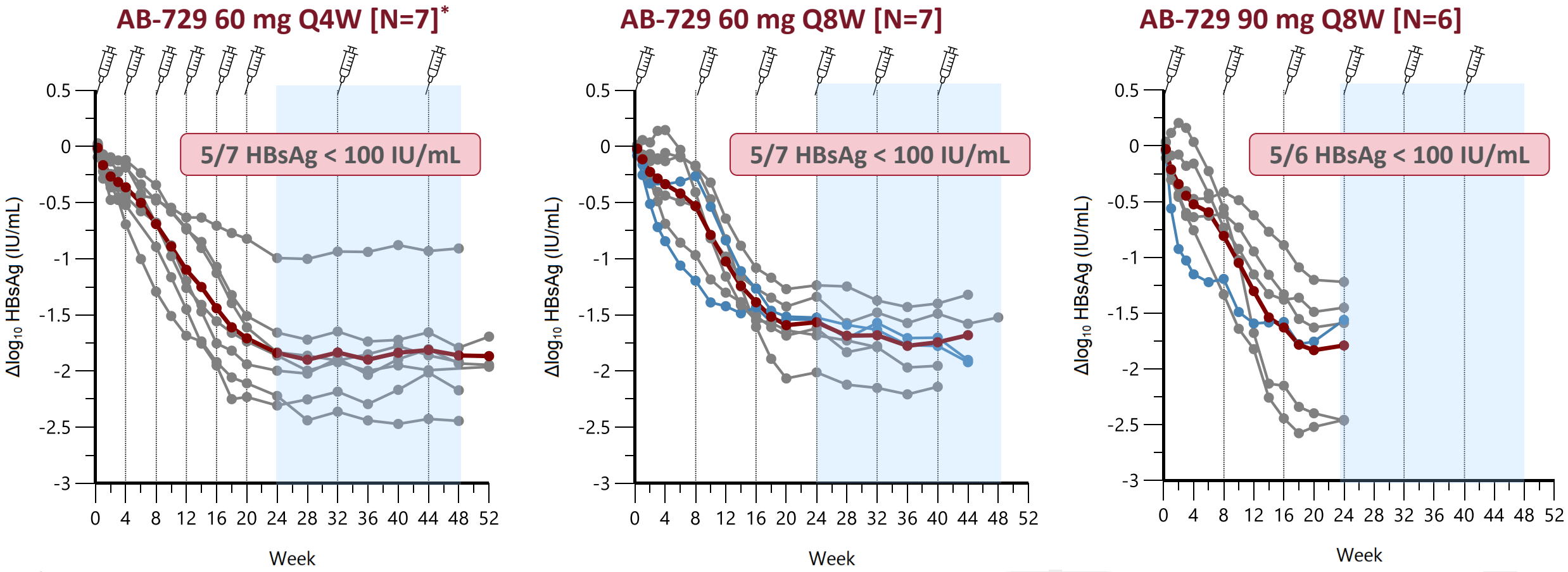
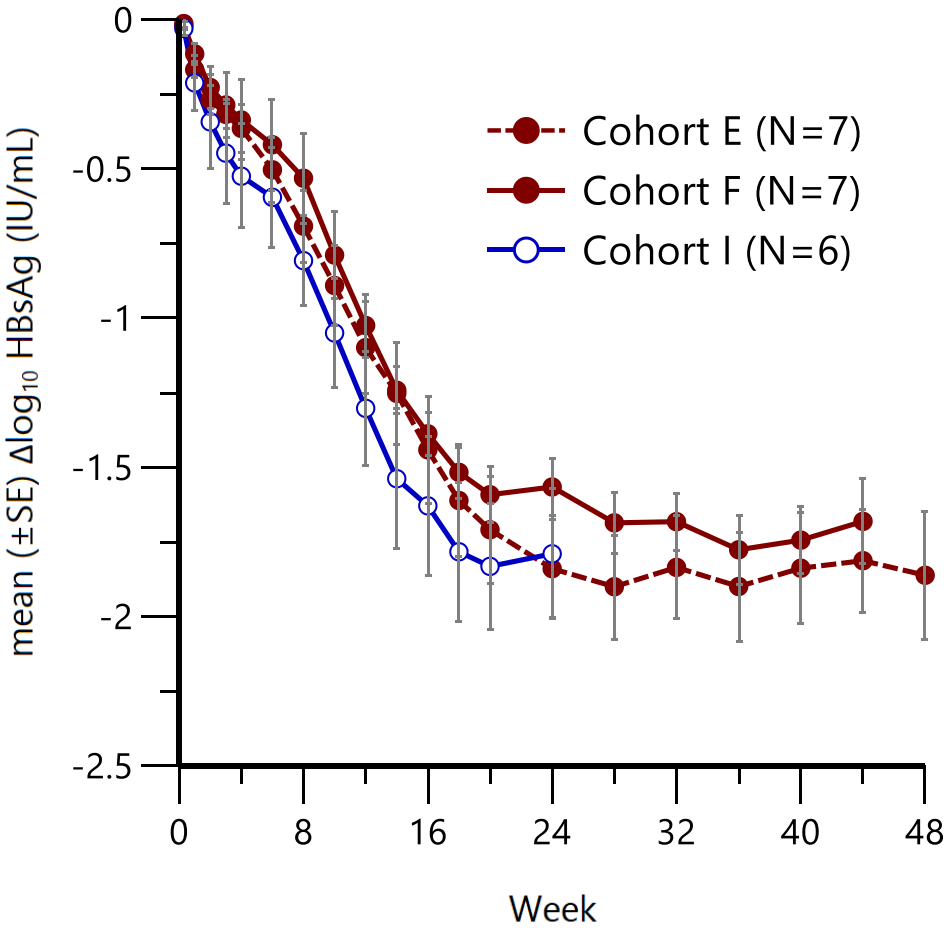
# Repeat dosing of AB-729 60 mg and 90 mg results in comparable HBsAg decline profiles

*Plateau in response observed around Week 20, regardless of dose or dosing interval*




*Due to the prolonged pharmacodynamic activity observed after a single dose of AB-729 (Yuen, AASLD 2020), subjects switched to AB-729 60 mg Q12W after Week 20

# There are no differences in mean HBsAg response between AB-729 doses and dosing intervals to date




## Mean (range) ΔHBsAg with repeat dosing of AB-729

| Visit | Cohort E AB-729 60 mg Q4W‡ | Cohort F AB-729 60 mg Q8W | Cohort I AB-729 90 mg Q8W | *p* value between Cohorts |
|---|---|---|---|---|
| **Week 16** | **-1.44** (-0.71 to -1.95) | **-1.39** (-1.61 to -1.08) | **-1.63** (-0.89 to -2.44) | $p \geq 0.4$ |
| **Week 24** | **-1.84** (-0.99 to -2.31) | **-1.57** (-1.24 to -2.01) | **-1.79** (-1.22 to -2.46) | $p \geq 0.2$ |
| **Week 32** | **-1.84** (-0.94 to -2.36) | **-1.68** (-1.37 to -2.15) | --- | $p = 0.5$ |
| **Week 40** | **-1.84** (-0.88 to -2.47) | **-1.74** (-1.40 to -2.14) [N=6] | --- | $p = 0.7$ |
| **Week 48** | **-1.86** (-0.91 to -2.44) [N=6] | --- | --- | --- |

‡ subjects switched to AB-729 60 mg Q12W after Week 20 dose

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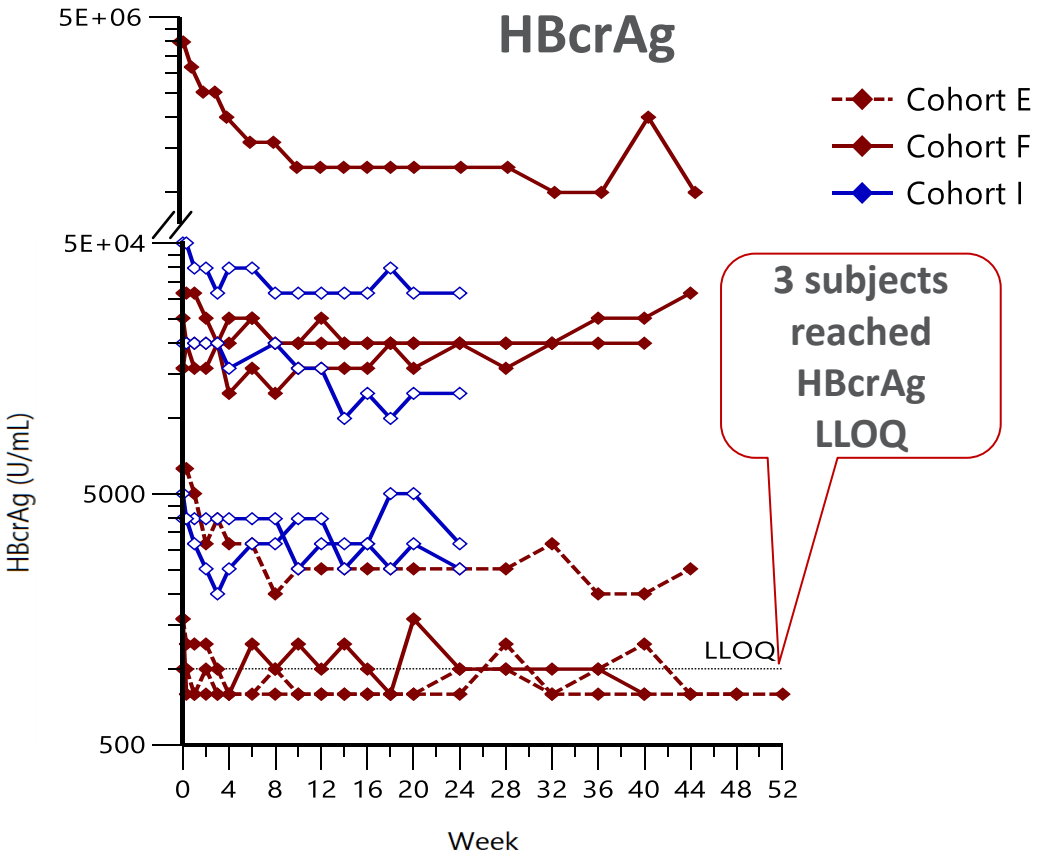
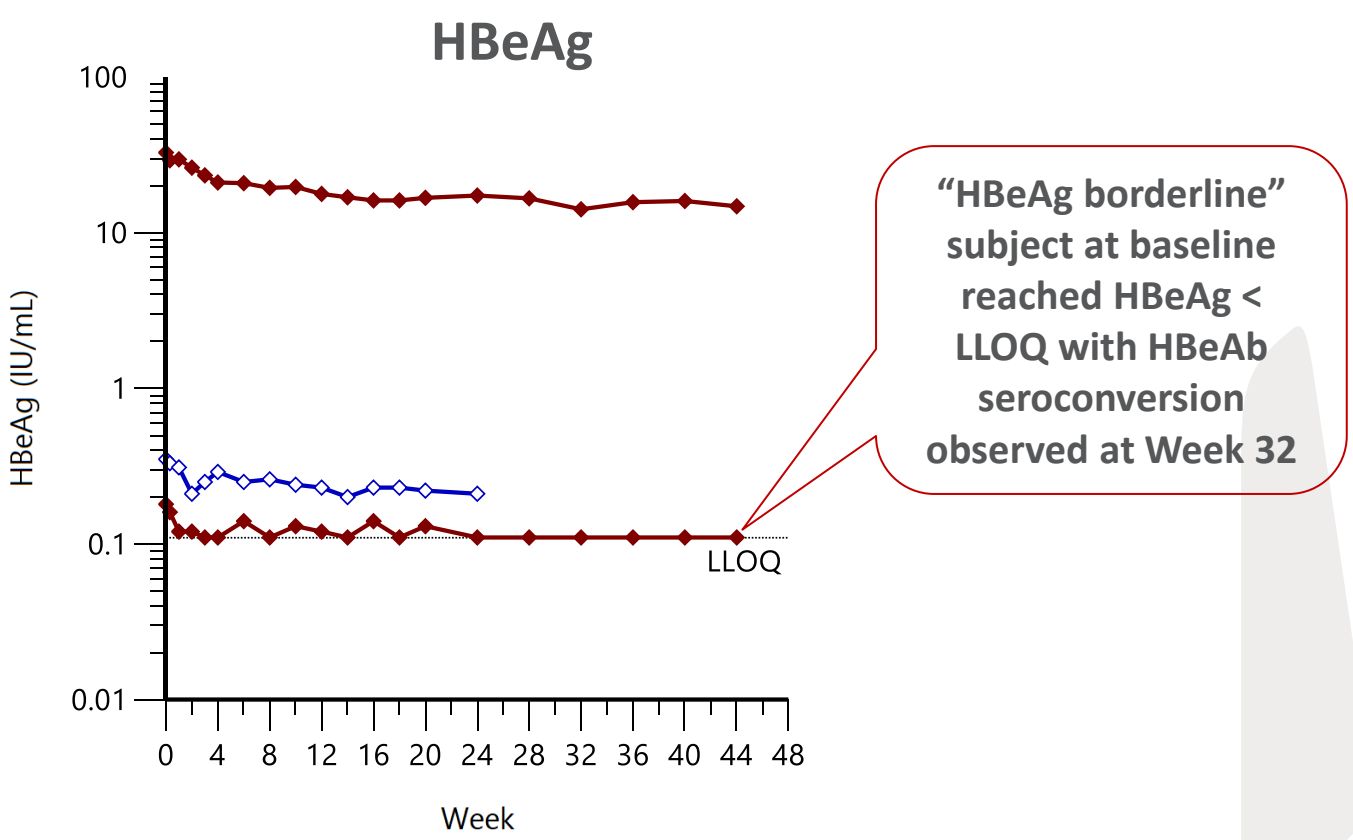
# Repeat dosing of AB-729 results in modest reductions in HBcrAg and HBeAg

*in subjects with quantifiable levels at baseline*




| Cohort | N | Mean (SE) Baseline HBcrAg | Max HBcrAg decline |
|---|---|---|---|
| E | 3 | 2,965 (1,681) U/mL | -0.5 $\log_{10}$ U/mL |
| F | 5 | 811,049 (792,522) U/mL | -0.6 $\log_{10}$ U/mL |
| I | 4 | 19,766 (10,756) U/mL | -0.3 $\log_{10}$ U/mL |

| Cohort | N | Baseline HBeAg (IU/mL) | Max HBcrAg decline to date |
|---|---|---|---|
| F | 2 | 0.18, 32.7 | -0.4 $\log_{10}$ U/mL |
| I | 1 | 0.35 | -0.2 $\log_{10}$ U/mL |

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# Repeat dosing of AB-729 was safe and well tolerated

- No SAEs or discontinuations due to AEs
- No Grade 3 or 4 TEAEs or laboratory abnormalities other than 1 transient Grade 3 CK elevation in a Cohort I subject
- All TEAEs were Grade 1 except 2 unrelated AEs of Grade 2 COVID-19 disease, one with fever
- Most common TEAEs were injection-site AEs
  - All were Grade 1 and none appear to be dose- or interval-dependent
- No ALT elevations were considered AEs by the Investigators, and no bilirubin or liver synthetic function changes were seen
  - ALT/AST elevations improved or stabilized with continued dosing
  - All Gr 2 elevations improved to Gr 1, 6 of 7 Gr 1 improved to Gr 0
- No clinically meaningful changes in ECGs or vital signs were seen

| Subjects, n (%) | Cohort E (60 mg Q4W*) [N=7] | Cohort F (60 mg Q8W) [N=7] | Cohort I (90 mg Q8W) [N=6] | TOTAL [N=20] |
|---|---|---|---|---|
| Subjects with any TEAE | 4 (57) | 5 (71) | 1 (17) | 10 (50) |
| SAEs | 0 | 0 | 0 | 0 |
| Subjects with related TEAEs (all Grade 1) | 2 (29) | 4 (57) | 1 (17) | 7 (35) |
| Most common related TEAEs (in ≥ 2 subjects): | | | | |
| Injection site pain | 0 | 2 (29) | 1 (17) | 3 (2)[#] |
| Injection site erythema | 2 (29) | 1 (14) | 0 | 4 (3)[#] |
| Injection site bruising | 2 (29) | 0 | 0 | 2 (2)[#] |
| Laboratory Abnormalities (in ≥ 2 subjects): | | | | |
| ALT elevation[‡] | | | | |
| Grade 1 | 2 (29) | 3 (43) | 2 (33) | 7 (35) |
| Grade 2 | 2 (29) | 1 (14)[†] | 2 (33) | 5 (25) |
| AST elevation[‡] | | | | |
| Grade 1 | 1 (14) | 3 (43) | 2 (33) | 6 (30) |
| Grade 2 | 1 (14) | 0 | 0 | 1 (5) |
| Sodium (low) | 1 (14) | 1 (14) | 1 (17) | 3 (15) |
| Glucose (low) | 0 | 2 (29) | 2 (33) | 4 (20) |
| Lipase | 0 | 1 (14) | 1 (17) | 2 (10) |
| Phosphate | 1 (14) | 0 | 1 (17) | 2 (10) |

TEAE: treatment-emergent adverse event; Grading criteria based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, V2.1

* subjects in Cohort E were switched to AB-729 60 mg Q12W after the Week 20 dose

[#] n, % is number of events out of 122 total AB-729 doses administered

[‡] for each subject only the highest grade is shown

[†] subject had history of pre-study Grade 1 ALT abnormalities and concurrent CK elevations

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# Key Take-Aways

- AB-729 60 mg Q4W, 60 mg Q8W, and 90 mg Q8W result in similar mean HBsAg declines to date
  - 15/20 subjects (75%) achieve HBsAg < 100 IU/mL
- A plateau in HBsAg response appears to occur around Week 20 of repeat dosing, regardless of AB-729 dose or dosing interval
- In subjects with quantifiable levels at baseline, modest declines in HBcrAg and HBeAg are observed with repeat dosing of AB-729
  - 3/12 subjects achieve unquantifiable HBcrAg levels after initiation of AB-729
  - 1 subject achieved unquantifiable HBeAg levels after initiation of AB-729 and subsequently seroconverted (HBeAb positive) at Week 32
- The doses and dose intervals of AB-729 explored were generally safe and well tolerated
- These data support the continued evaluation of AB-729 as the cornerstone of combination treatment to achieve functional cure of chronic HBV.

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# Acknowledgements

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We invite you to visit the following poster presentations for additional data on AB-729:

**PO-2822:** Inhibition of hepatitis B surface antigen by RNA interference therapeutic AB-729 in chronic hepatitis B patients correlates with suppression of all HBsAg isoforms and HBV RNA

**PO-2823:** Inhibition of hepatitis B surface antigen in chronic hepatitis B subjects by RNA interference therapeutic AB-729 is accompanied by upregulation of HBV-specific T cell activation markers

**PO-2879:** A single dose of the GalNAc-siRNA, AB-729, results in prolonged reductions in HBsAg, HBcrAg, HBV DNA and HBV RNA in the absence of nucleos(t)ide analogue therapy in HBeAg negative subjects with chronic hepatitis B infection

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