# LB/O99: 48 weeks of AB-729 + nucleos(t)ide analogue (NA) therapy results in profound, sustained HBsAg declines in both HBeAg+ and HBeAg- subjects which are maintained in HBeAg- subjects who have discontinued all therapy

**Man-Fung Yuen[1], Jacinta Holmes[2], Simone I Strasser[3], Apinya Leerapun[4], Wattana Sukeepaisarnjaroen[5], Pisit Tangkijvanich[6], Varun Sharma[7], Elina Medvedeva[7], Emily P Thi[8], Gastón Picchio[7], Timothy Eley[7], Karen D Sims[7]**

[1]The University of Hong Kong, Hong Kong, [2]St. Vincent's Hospital, Melbourne, [3]Royal Prince Alfred Hospital, Sydney, Australia, [4]Chiang Mai University, Chiang Mai, [5]Khon Kaen University, Khon Kaen, [6]Chulalongkorn University, Bangkok, Thailand, [7]Clinical Development, Arbutus Biopharma, Warminster, United States [8]Research/Discovery, Arbutus Biopharma, Warminster, United States


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# Disclosures - Man-Fung Yuen, D.Sc., M.D., Ph.D.

- Consultant for AbbVie, Aligos Therapeutics, AiCuris, Antios Therapeutics, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosciences, Clear B Therapeutics, Dicerna Pharmaceuticals, Finch Therapeutics, Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Immunocore, Janssen, Roche, Sysmex Corporation, Tune Therapeutics, Vir Biotechnology and Visirna Therapeutics

# Background

- There is an unmet medical need for new finite HBV therapies that have the potential to provide a functional cure for CHB
- AB-729 is a subcutaneously administered *N*-Acetylgalactosamine(GalNAc)-conjugated, single trigger, pan-genotypic siRNA therapeutic that blocks all HBV RNA transcripts, including HBx, resulting in suppression of viral replication and all viral antigens
- In the AB-729-001 Phase 1a/1b study in HBV DNA positive and negative CHB subjects, AB-729 administered every 4, 8, or 12 weeks resulted in robust mean HBsAg declines of -1.8 $\log_{10}$ to -2.6 $\log_{10}$ from baseline across all cohorts at end of treatment
- Here we report following:
  - Further follow-up data for subjects who completed 48 weeks of AB-729 treatment and remained on NA therapy for the 48 week follow-up period
  - Additional follow-up for subjects with HBsAg <100 IU/mL who stopped NA therapy at least 24 weeks post-last dose of AB-729

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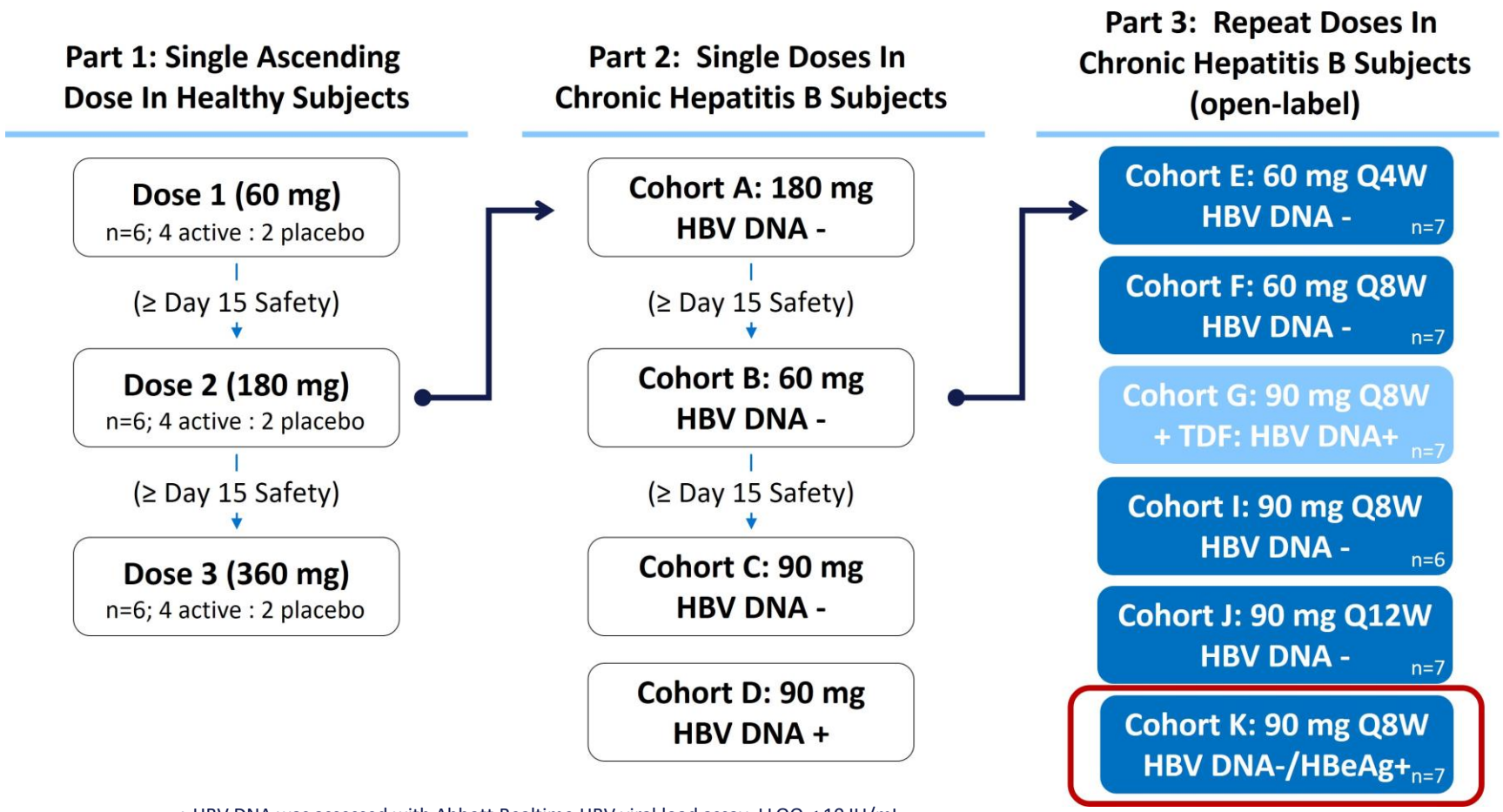
# Study Design – AB-729-001




- HBV DNA was assessed with Abbott Realtime HBV viral load assay, LLOQ < 10 IU/mL
- HBsAg was assessed with Roche Elecsys HBsAg II Quant II, LLOQ < 0.07 IU/mL
- HBeAg was assessed with Abbott Architect HBeAg Quant, LLOQ < 0.11 IU/mL
- HBsAb was assessed with Siemens Advia Centaur aHBs2, LLOQ < 5.0 mIU/mL
- ALT upper limit of normal (ULN) = 48 U/L for males, 43 U/L for females

- Cohorts E, F, I, and J enrolled HBV DNA- subjects on stable NA therapy.
- Cohort G enrolled HBV DNA+ subjects who began treatment with TDF concurrently with AB-729 on Study Day 1
- Cohort K enrolled HBV DNA-, HBeAg+ subjects only
- Part 3 subjects who completed 48 weeks of AB-729 treatment and met protocol-defined NA stopping criteria (assessed at least 24 weeks after the last dose of AB-729) were permitted to stop NA therapy
  - ALT <2 × ULN,
  - Undetectable (target not detected, TND) HBV DNA,
  - HBeAg negative, and
  - HBsAg <100 IU/mL at two consecutive visits

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# Demographics and Baseline Characteristics

| Baseline Measure | Cohort E* 60 mg Q4W (N=7) | Cohort F 60 mg Q8W (N=7) | Cohort I 90 mg Q8W (N=6)^ | Cohort J 90 mg Q12W (N=7) | Cohort K/HBeAg+ 90 mg Q8W (N=7) | Cohort G/HBV DNA+ 90 mg Q8W (N=7) |
|---|---|---|---|---|---|---|
| **Age in years, mean (range)** | 45.1 (33 – 63) | 44.0 (31 – 59) | 45.7 (38 – 54) | 44.3 (35 – 61) | 41.4 (21 – 57) | 43.9 (34 – 50) |
| **Male gender, n (%)** | 4 (57%) | 4 (57%) | 4 (67%) | 5 (71%) | 4 (57%) | 3 (43%) |
| **Race, n (%)** | | | | | | |
| **Asian** | 1 (14%) | 5 (71%) | 5 (83%) | 4 (57%) | 6 (86%) | 6 (86%) |
| **Black** | 0 | 1 (14%) | 0 | 0 | 0 | 0 |
| **White** | 6 (86%) | 1 (14%) | 1 (17%) | 3 (43%) | 0 | 1 (14%) |
| **Pacific Islander** | 0 | 0 | 0 | 0 | 1 (14%) | 0 |
| **ALT (U/L), mean (SD)** | 22.4 (10.52) | 23.4 (15.22) | 26.0 (10.20) | 20.1 (7.22) | 25.1 (8.9) | 32.7 (15.81) |
| **NA therapy at entry, n (%)** | | | | | | |
| **ETV** | 1 (14%) | 2 (29%) | 3 (50%) | 1 (14%) | 2 (29%) | N/A (TDF started on Day 1) |
| **TDF/TAF** | 6 (86%) | 5 (71%) | 3 (50%) | 6 (86%) | 5 (71%) | |
| **HBeAg negative, n (%)** | 7 (100%) | 6 (71%) | 5 (83%) | 4 (57%) | **19.64 IU/mL‡ (range 0.3 – 98.2)** | 7 (100%) |
| **HBsAg (IU/mL), mean (range)** | 5,372 (584 – 11,761) | 5,354 (667 – 18,605) | 4,691 (338 – 19,017) | 6,911 (309 – 25,345) | 2,221 (545 – 5,273) | 1,818 (277 – 4,723) |

ALT: alanine aminotransferase; *Subjects in Cohort E switched to AB-729 60 mg Q12W after Week 20 dose; ^N = 6, 2 subjects with protocol violations on Day 1 were excluded from the analysis; ‡Data shown are baseline mean (range) HBeAg levels (LLOQ < 0.11 IU/mL).

- Baseline characteristics were similar across Cohorts, with slightly more males than females and mostly Asian subjects represented; most subjects were HBeAg-negative outside of Cohort K; mean baseline HBsAg levels were slightly lower in Cohorts K and G

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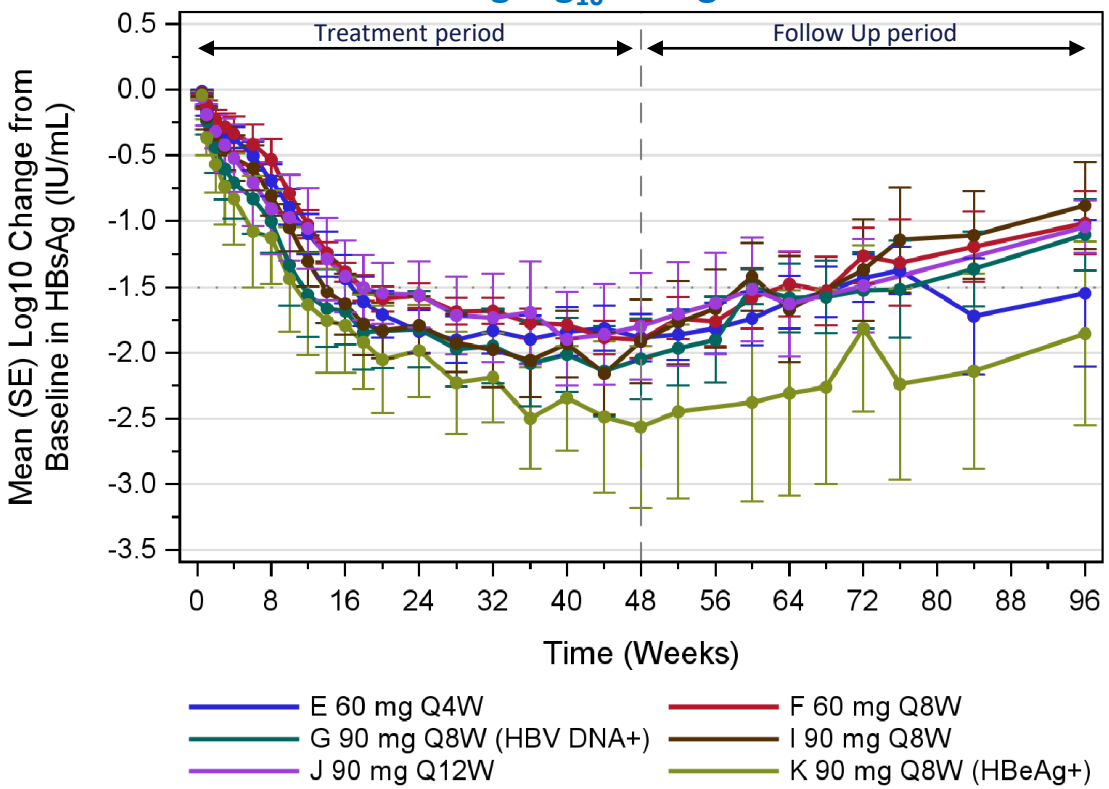
# Comparable mean HBsAg declines were observed in all Cohorts

## Mean HBsAg $log_{10}$ change from baseline




## Mean HBsAg $log_{10}$ IU/mL change from baseline at key timepoints

| Visit Mean (SE) | Cohort E (N=7) | Cohort F (N=7) | Cohort I (N=6) | Cohort J (N=7) | Cohort K (N=7) | Cohort G (N=7) |
|---|---|---|---|---|---|---|
| **Baseline** | 3.51 (0.20) | 3.53 (0.17) | 3.36 (0.23) | 3.37 (0.28) | 3.23 (0.14) | 3.14 (0.14) |
| **Treatment Week 12** | -1.10 (0.15) | -1.02 (0.11) | -1.30 (0.19) | -1.06 (0.31) | -1.63 (0.39) | -1.56 (0.32) |
| **Treatment Week 24** | -1.84 (0.16) | -1.57 (0.09) | -1.79 (0.22) | -1.56 (0.25) | -1.99 (0.35) | -1.82 (0.29) |
| **Treatment Week 48** | -1.89 (0.18) | -1.90 (0.14) | -1.91 (0.32) | -1.80 (0.41) | -2.57 (0.61) | -2.05 (0.31) |
| **Follow Up Week 12** | -1.74 (0.20) | -1.59 (0.23) | -1.42 (0.26) | -1.52 (0.40) | -2.38 (0.75) | -1.50 (0.13) |
| **Follow Up Week 24** | -1.43 (0.18) | -1.26 (0.21) | -1.37 (0.39) | -1.49 (0.35) | -1.82 (0.63) | -1.53 (0.29) |
| **Follow Up Week 48** | -1.55 (0.56) | -1.01 (0.24) | -0.88 (0.33) | -1.04 (0.20) | -1.86 (0.70) | -1.10 (0.27) |

Data shown are for a minimum of 5 subjects/timepoint. Last dose of AB-729: Cohort E, Week 44; Cohorts F, I, G, K: Week 40; Cohort J: Week 36.

- All Cohorts achieved at least a -1.8 $log_{10}$ decline in mean HBsAg at the end of the treatment period (Week 48)
- Mean HBsAg levels remained below baseline values at Follow Up Week 48
- There were no significant differences in mean HBsAg declines between the 60 mg and 90 mg doses or between different dosing intervals
- AB-729 was well-tolerated at all dose levels and intervals, with no treatment discontinuations due to AEs or treatment-related Grade 3 or 4 AEs

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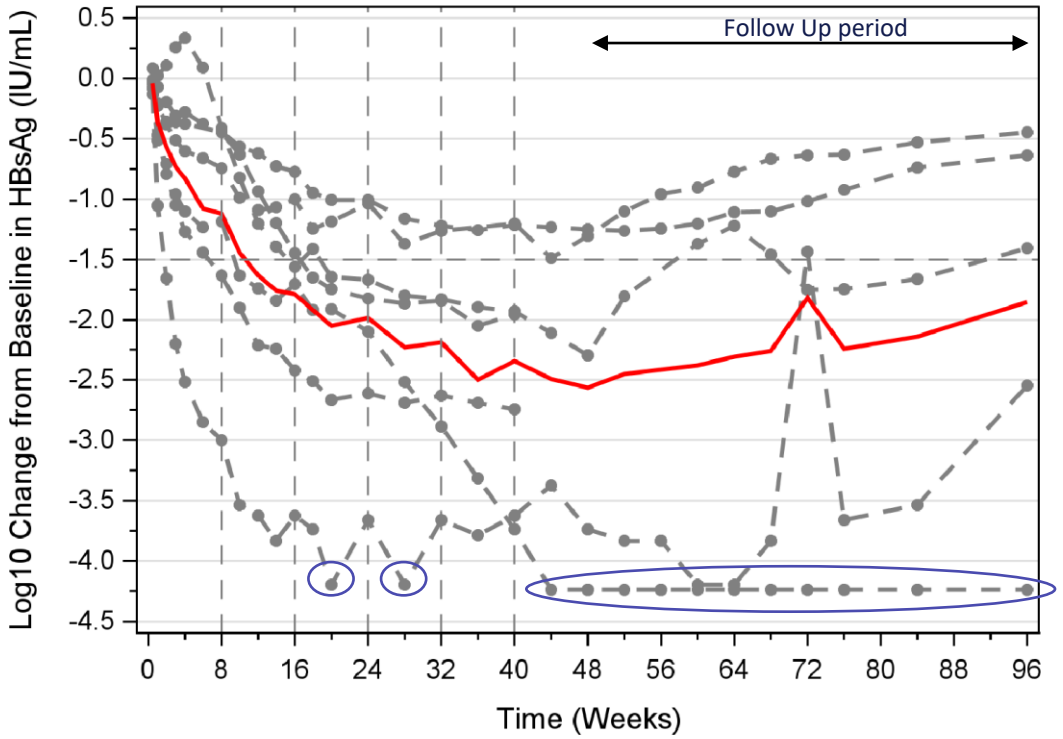
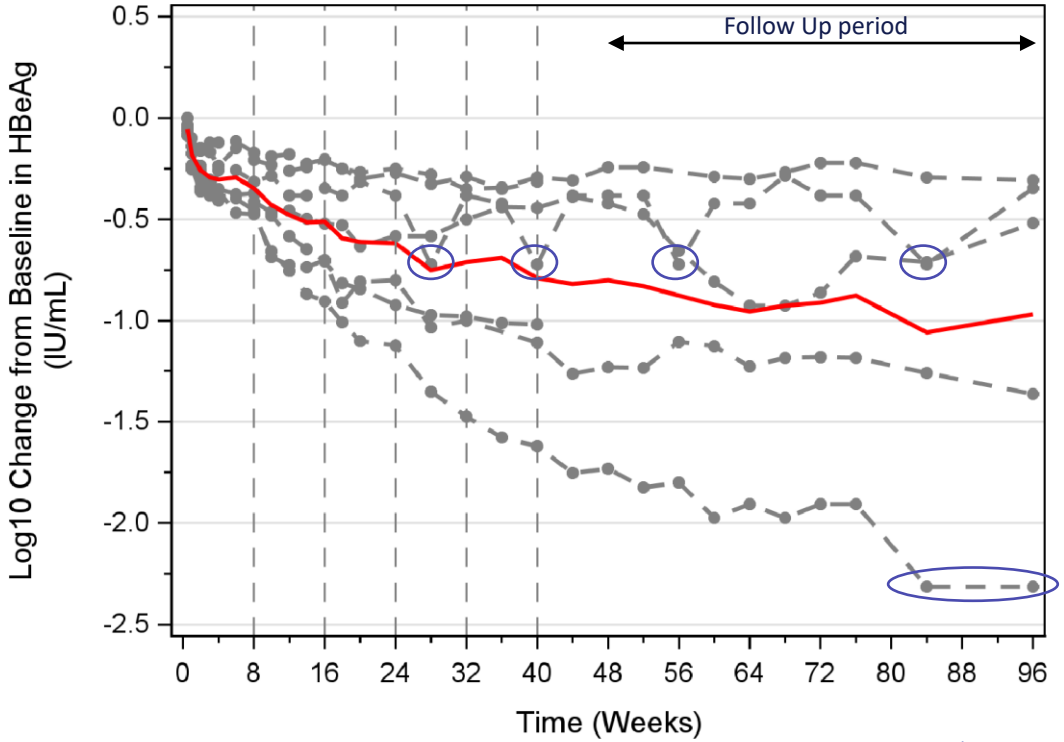
# AB-729 reduced both HBsAg and HBeAg in Cohort K (HBeAg+) subjects

**HBsAg $log_{10}$ change from baseline**




Dashed lines indicate AB-729 doses. Cohort mean shown in red; HBsAg LLOQ <0.07 IU/mL; circles denote values <LLOQ.

**HBeAg $log_{10}$ change from baseline**




Dashed lines indicate AB-729 doses. Cohort mean shown in red; HBeAg LLOQ <0.11 IU/mL; circles denote values <LLOQ.

- 1 subject achieved HBsAg <LLOQ (<0.07 IU/mL) with detectable anti-HBs and HBeAg <LLOQ (<0.11 IU/mL)
- 2 other subjects achieved either HBsAg or HBeAg <LLOQ during the study
- Mean log10 decline in HBeAg was ~1.0 $log_{10}$ at last follow up visit, despite low HBeAg at baseline in some subjects

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# HBV DNA and HBsAg reductions persist in subjects who discontinued NA therapy

## Baseline characteristics of NA discontinuation subjects

| Baseline Measure | Pre-Study HBV DNA- (NA Suppressed) | | | | | Pre-Study HBV DNA+ | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Subj 46 | Subj 51 | Subj 52 | Subj 53 | Subj 61 | Subj 56 | Subj 58 | Subj 59 | Subj 60 |
| Age (years) | 35 | 49 | 36 | 61 | 56 | 52 | 50 | 36 | 46 |
| Gender | F | M | M | F | F | F | M | M | F |
| Race | Asian | Black | Asian | Asian | Asian | Asian | Asian | Asian | Asian |
| Study Cohort | E | F | F | F | I | G | G | G | G |
| NA therapy at study entry | ETV | ETV | TDF | TDF | ETV | none | none | none | none |
| Total duration of NA therapy | 9 y, 7 m | 6 y, 2 m | 17 y | 7 y, 5 m | 6 y, 5 m | 1 y, 6 m* | 1 y, 6 m* | 1 y, 6 m* | 1 y, 6 m* |
| Baseline HBsAg (IU/mL) | 1392 | 6765 | 1888 | 2368 | 2021 | 277 | 1397 | 1338 | 1128 |

* All Cohort G subjects started TDF on Study Day 1; y = year, m= month

Protocol-defined NA Restart criteria:
- Persistent ALT elevations ≥2 × baseline, AND ≥2 – 5 × ULN, AND HBV DNA >2000 IU/mL for 12 weeks
- Persistent ALT elevations ≥2 × baseline, AND ≥5 – 10 × ULN, AND HBV DNA >2000 IU/mL for 4 weeks
- HBV DNA >20,000 IU/mL regardless of ALT level, confirmed by repeat
- ALT >10 x ULN confirmed by repeat
- ALT >baseline and >ULN, AND:
  - increased direct or total bilirubin ≥2 × ULN and ≥2 × baseline confirmed by repeat, OR
  - INR increase of ≥0.5 from baseline, confirmed by repeat

- 7 of 9 (78%) subjects remain off NA therapy
  - These 7 subjects have been off NA therapy for 44-64 weeks and completed AB-729 treatment over 1½ years ago
  - HBV DNA in these subjects remains low
  - HBsAg remains between -0.8 and -1.6 $\log_{10}$ IU/mL below baseline values
  - No ALT flares have occurred
- Two of 9 subjects restarted NA therapy
  - As previously reported, Subject 53 restarted NA therapy at Investigator's request after the NA d/c FU Week 20 visit (HBV DNA = 4,670 IU/mL)
  - Subject 58 had confirmed HBV DNA > 20,000 IU/mL and NA therapy was restarted at NA d/c FU Week 32
  - No ALT flares or other safety signals were observed in either subject

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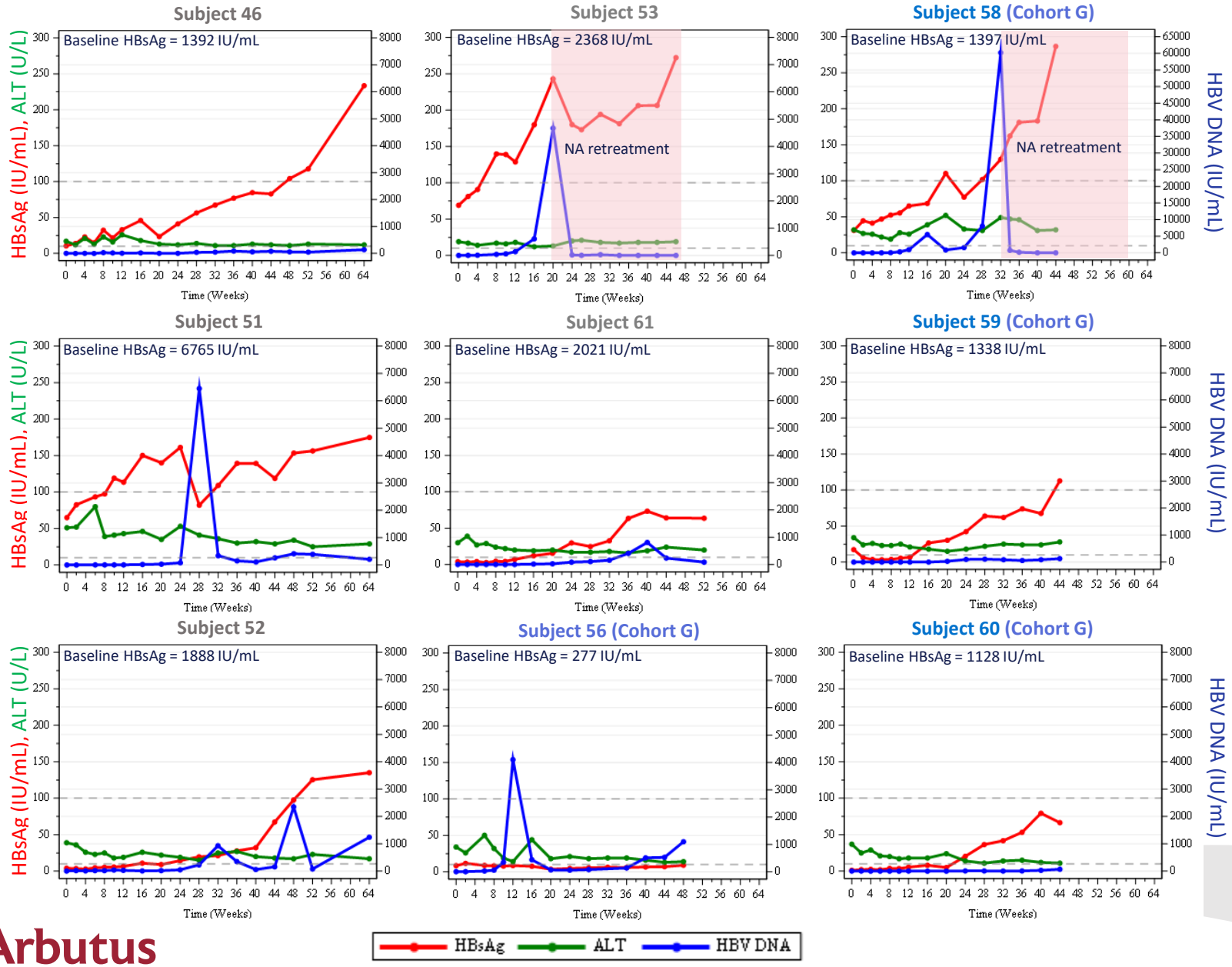
# HBV DNA suppression after NA cessation suggests immune control




- NA discontinuation post-AB-729 treatment appears well tolerated with no ALT flares
- Most subjects have maintained low HBV DNA levels off treatment, despite occasional blips
- HBsAg remains well below baseline levels in all subjects

Time = weeks post-NA discontinuation; Time 0 is at least 24 weeks after last AB-729 dose

HBsAg LLOQ = 0.07 IU/mL, <LLOQ defined as 0.035 IU/mL

HBV DNA LLOQ = 10 IU/mL, <LLOQ defined as 5 IU/mL and TND defined as 1 IU/mL

ALT ULN = 48 U/L (males) or 43 U/L (females)

Dashed lines represent HBsAg levels of 100 IU/mL and 10 IU/mL

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# Conclusions

- AB-729 treatment produced robust and comparable declines in HBsAg regardless of dose, dosing interval, baseline HBeAg+ or HBV DNA+ status
- HBsAg declines in most subjects persist for at least a year after the last dose of AB-729
- AB-729 was well-tolerated through 48 weeks of treatment, regardless of dose or dosing interval
- Discontinuation of all therapy in AB-729-treated subjects who achieved HBsAg <100 IU/mL is well tolerated and has led to continued low levels of HBV DNA and HBsAg in most subjects
  - No ALT flares have been observed
  - These results suggest ongoing host immune control in the absence of therapy
  - Subjects will be followed for up to 3 years to monitor for functional cure
- AB-729 is in Phase 2 clinical development in combination with other agents, including pegylated interferon alfa-2a (NCT04980482) and VTP-300, an HBV antigen-specific immunotherapeutic (ACTRN12622000317796).

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**Participating Sites:**

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**Australia:**

- Jacinta Holmes, St. Vincent's Hospital, Melbourne
- Simone Strasser, Royal Prince Alfred Hospital, Sydney

**Hong Kong:**

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- Pisit Tangkijvanich, King Chulalongkorn Memorial Hospital, Bangkok
- Apinya Leerapun, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai
- Wattana Sukeepaisarnjaroen, Srinagarind Hospital, Khon Kaen

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- Yoon Jun Kim, Seoul National University Hospital, Seoul
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