# Continued suppression of viral markers observed following discontinuation of nucleos(t)ide analogue therapy in chronic hepatitis B subjects with low hepatitis B surface antigen levels after 48 weeks of treatment with AB-729

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Arbutus BIOPHARMA Curing Chronic Hepatitis B

## BACKGROUND

- Current therapies for chronic hepatitis B (CHB) slow or prevent the development of HBV-related liver complications, but do not typically lead to a cure.[1,2,3] Thus, 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 RNA interference therapeutic that blocks all HBV RNA transcripts, including HBx, resulting in suppression of viral replication and all viral antigens. AB-729 is in Phase 2 clinical development for the treatment of CHB in combination with other agents.
- AB-729-001 is a 3-part study examining the safety and pharmacodynamics (PD) of single and repeat doses of AB-729 in healthy subjects and CHB subjects (both untreated and virologically-suppressed on nucleos(t)ide analogue [NA] therapy), and preliminary data have been reported previously.[4,5,6,7]
- An amendment to AB-729-001 permitted the optional discontinuation of NA therapy in Part 3 subjects who completed 48 weeks of AB-729 treatment and who met protocol-defined NA stopping criteria assessed at least 24 weeks after the last dose of AB-729.
- Here we report preliminary safety and virology data from the subjects who have elected to participate in the NA discontinuation period to date.
- Follow up data for the remainder of the subjects in study AB-729-001 who remained on NA therapy for the duration of follow-up is presented in Poster SAT443, and additional immunology data for a subset of study subjects is presented in Posters SAT396 and SAT397.

## MATERIALS AND METHODS

### Figure 1: AB-729-001 Study Design (Part 3)

**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

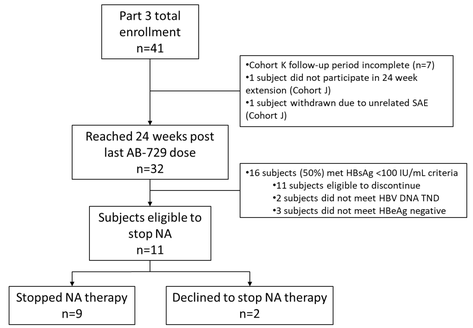
- Study AB-729-001 is ongoing; however AB-729 dosing is complete
- Cohorts E, F, I, and J enrolled HBeAg positive and negative, HBV DNA- subjects on stable NA therapy. Cohort K enrolled HBeAg positive subjects only
- Cohort G enrolled HBeAg positive and negative, HBV DNA+ subjects who began treatment with TDF concurrently with AB-729 on Study Day 1
- The option to stop NA therapy was limited to those subjects that completed 48 weeks of AB-729 treatment (total number of AB-729 doses varied according to dosing schedule) via an optional 24 week treatment extension
- Eligibility was determined using the following criteria on or after 24 weeks post last dose of AB-729:
  - ALT <2 × ULN, and
  - Undetectable (target not detected, TND) HBV DNA, and
  - HBeAg negative, and
  - At least one of the following:
    - HBsAg undetectable for at least 24 weeks after the last dose of AB-729
    - HBsAg <100 IU/mL at two consecutive visits at least 24 weeks after the last dose of AB-729
    - HBsAb positive for at least 24 weeks after the last dose of AB-729
- After stopping NA, subjects were evaluated every 2 weeks for the first 12 weeks, then monthly
- Clinical laboratory testing and HBV parameters were collected at each visit
- NA therapy could be restarted if subjects met protocol-defined criteria

Study assay methods/cutoffs:

- 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
- HBcrAg was assessed with Fujirebio Lumipulse G HBcrAg, LLOQ = 3.0 log U/mL
- HBV RNA was assessed with Abbott RUO HBV RNA V1.0 or 2.0, LLOQ = 1.65 $\log_{10}$ U/mL (V1.0) or 0.49 $\log_{10}$ U/mL (V2.0)
- ALT upper limit of normal (ULN) = 48 U/L for males, 43 U/L for females

## RESULTS

### Figure 2: Subject Disposition




- Subjects with at least 4 weeks of follow-up data are presented (n=5); duration of subject follow-up ranged from 4 weeks to 24 weeks post-NA discontinuation

### Table 1: Baseline Characteristics

| Baseline Measure | Subject 46 | Subject 51 | Subject 52 | Subject 53 | Subject 61 | Subject 56 | Subject 58 | Subject 59 | Subject 60 |
|---|---|---|---|---|---|---|---|---|---|
| Age (years) | 35 | 49 | 36 | 61 | 56 | 52 | 50 | 36 | 46 |
| Gender | Female | Male | Male | Female | Female | Female | Male | Male | Female |
| 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 |

- All subjects who discontinued NAs were HBeAg negative at study entry

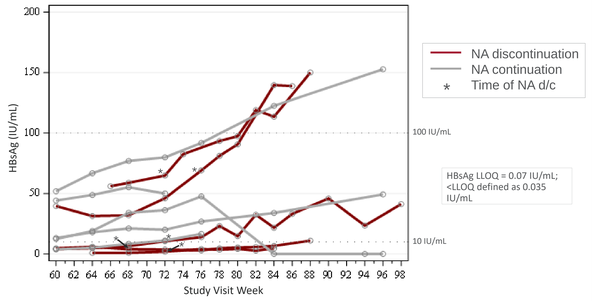
### Table 2: HBV Markers

| HBV Parameter | Subject 46 | Subject 51 | Subject 52 | Subject 53 | Subject 61 | Subject 56 | Subject 58 | Subject 59 | Subject 60 |
|---|---|---|---|---|---|---|---|---|---|
| **HBsAg (IU/mL)** | | | | | | | | | |
| Study Day 1 | 1392 | 6765 | 1888 | 2368 | 2021 | 277 | 1397 | 1338 | 1128 |
| Week 48/EOT | 5.00 | 29.61 | 9.54 | 22.76 | 1.64 | 6.61 | 15.15 | 1.46 | 0.51 |
| Last Visit prior to NA d/c | 10.53 | 64.90 | 3.95 | 69.06 | 3.99 | 8.40 | 31.09 | 17.31 | 1.38 |
| Last available post-NA d/c | 41.22 | 150.1 | 10.97 | 138.9 | 4.58 | N/A | N/A | N/A | N/A |
| **HBcrAg (log U/mL)** | | | | | | | | | |
| Study Day 1 | 3.8 | <3.0 | 3.2 | 4.2 | 3.7 | 4.2 | 4.0 | <3.0 | 3.1 |
| Week 48/EOT | 3.4 | <3.0 | 3.0 | 4.4 | 3.4 | 3.6 | 4.0 | <3.0 | <3.0 |
| Last Visit prior to NA d/c | 3.4 | <3.0 | 3.0 | 4.5 | 3.5 | 4.3 | 4.0 | <3.0 | 3.0 |
| Last available post-NA d/c | 3.4 | <3.0 | 3.1 | 4.5 | 3.6 | N/A | N/A | N/A | N/A |
| **HBV RNA ($\log_{10}$ U/mL)** | | | | | | | | | |
| Study Day 1 | 2.07 | TND | <LLOQ | <LLOQ | N/A | 3.34 | 2.76 | 1.15 | 1.74 |
| Week 48/EOT | TND | TND | 0.70 | TND | TND | TND# | TND‡ | 0.78‡ | TND‡ |
| Last Visit prior to NA d/c* | 1.29 | 1.07 | 1.20 | TND | 1.43 | N/A | N/A | N/A | N/A |
| Last available post-NA d/c | 1.16 | 1.31 | 1.36 | 1.08 | 1.09 | N/A | N/A | N/A | N/A |

*Last available HBV RNA timepoint was Treatment Extension Week 44^ or 40‡; y = year; m = month; d/c = discontinuation; EOT = end of treatment

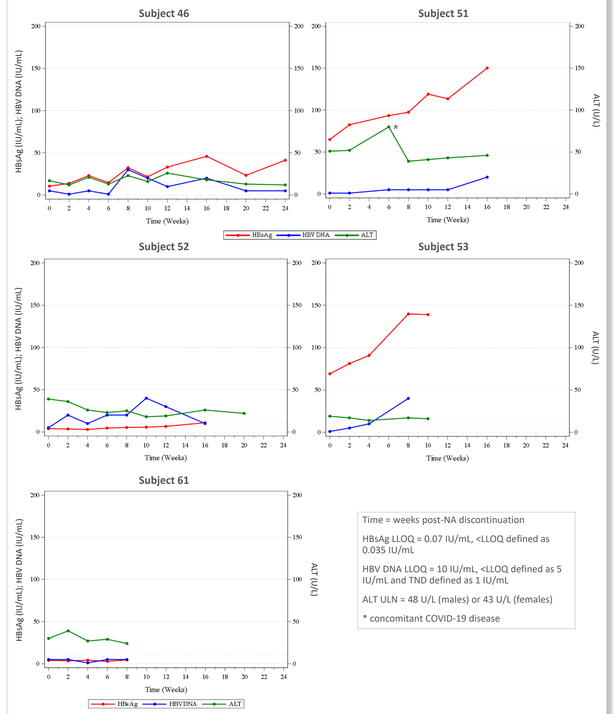
- No subjects have met criteria to restart NA therapy or had evidence of viral (confirmed HBV DNA > 2000 IU/mL) or clinical relapse (confirmed HBV DNA > 2000 IU/mL plus ALT ≥ 2 × ULN and 2 × baseline)
- Three adverse events have been reported in 2 subjects during the follow-up period, all related to COVID-19 disease
- One subject had ALT of 80 U/L at the Week 6 visit coincident with COVID-19 disease, HBV DNA was <LLOQ; ALT returned to normal at Week 8 and HBV DNA remained <LLOQ
  - all other ALT values for other subjects have been < ULN

### Figure 3: HBsAg levels ≥ 24 weeks post-last AB-729 dose in HBeAg-negative subjects who reached <100 IU/mL




- Data shown are for NA discontinuation subjects (red, n=5) and comparable HBeAg-negative subjects with HBsAg <100 IU/mL 24 weeks post-last dose of AB-729 that did not discontinue NA (gray, n=5)
- Most subjects maintained HBsAg <100 IU/mL for the available follow-up period
- Discontinuation of NAs did not appear to negatively impact HBsAg kinetics

### Figure 4: Individual plots of HBV DNA, HBsAg and ALT post-NA discontinuation




- Data shown are individual subject plots of HBsAg (red) and HBV DNA (blue) vs ALT (green) over times since NA discontinuation
- No subjects have met viral or clinical relapse criteria or restarted NA
- HBV DNA has transiently increased in some subjects and subsequently decreased with no intervention

## CONCLUSIONS

- AB-729 treatment for 48 weeks at varying doses and intervals led to continued HBsAg declines to <100 IU/mL in 50% of subjects 24 weeks after the last dose of AB-729
  - Eleven of these 16 subjects met protocol-defined NA stopping criteria
- No evidence of viral or clinical relapse has been detected in the first 5 subjects to discontinue NA therapy with at least 8 - 24 weeks of follow up data available
  - No subjects have restarted NA therapy
  - HBsAg remains well below pre-study levels in all subjects
- Additional data is needed to determine the value of HBV RNA and HBcrAg in predicting outcomes once NA therapy is discontinued
- Discontinuation of NA therapy for up to 24 weeks has been safe and well-tolerated to date with no ALT flares observed
- Subjects will continue to be followed every 2-4 weeks for 1 year after stopping NA therapy, and longer term follow up is being amended into the protocol to monitor for sustained viral response and functional cure.

## REFERENCES

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Please see Posters SAT395, SAT396, SAT397, and SAT443 for additional data regarding AB-729 and Study AB-729-001.

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