Hepatitis B viral control maintained during extended follow up of HBeAg- chronic hepatitis B (CHB) subjects who discontinued nucleos(t)ide analogue (NA) therapy after completion of AB-729 treatment, and in HBeAg+ subjects still on NA therapy

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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 siRNA 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 from all 3 study parts including Cohort K (a dedicated HBeAg+ cohort) have been reported previously.[4,5,6]
- An amendment to AB-729-001 permitted the optional discontinuation of NA therapy in Part 3 CHB 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. Preliminary data for 5 of the 9 subjects who chose to participate were reported previously.[7]
- Here we report the following:
  - post-treatment virology data from Cohort K (HBeAg+) subjects who have now all completed the AB-729 dosing period
  - extended follow-up data from the 9 subjects from Cohorts E, F, G and I who elected to participate in the NA discontinuation period

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+ and HBeAg-, HBV DNA- subjects on stable NA therapy. Cohort K enrolled HBV DNA-/HBeAg+ subjects only
- Cohort G enrolled HBeAg+ and HBeAg-, 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 **at least 24 weeks post-last dose of AB-729**:
  - ALT <2 × ULN, and
  - Undetectable (target not detected, TND) HBV DNA, and
  - HBeAg negative, and
  - HBsAg <100 IU/mL at two consecutive visits
- 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 will be restarted if subjects meet protocol-defined 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.
- Clinical/biochemical relapse is defined as confirmed HBV DNA >2000 IU/mL plus ALT ≥2 × ULN

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
- 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

RESULTS: COHORT K (HBeAg+)

Table 1: Baseline Characteristics

Baseline Measure[#]	Cohort K (N=7)
Age in years, mean (range)	41.4 (21 – 57)
Male gender, n (%)	4 (57)
BMI, mean (SD)	25.0 (4.7)
Race, n (%)	
Asian	6 (86)
Black	0
White	0
Pacific Islander	1 (14)
ALT (U/L), mean (SD)	25.1 (8.9)
HBeAg (IU/mL), mean (range)	19.64 (0.3 – 98.2)
HBsAg (IU/mL), mean (range)	2,221 (545 – 5,273)

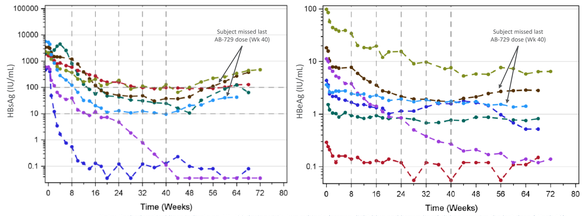
[#] Genotype not determined

Table 2: HBsAg Change from Baseline

Nominal Visit	Cohort K (N=7)
Baseline	3.23 (0.14)
Week 12	-1.63 (0.39)
Week 24	-1.99 (0.35)
Week 36	-2.50* (0.39)
Week 48	-2.57[#] (0.61)
Week 12 Post Last Dose	-2.45[#] (0.66)
Week 24 Post Last Dose	-2.31[#] (0.78)

Data shown as mean (SE) $\log_{10}$ IU/mL; HBsAg LLOQ = 0.07 IU/mL, <LLOQ defined as 0.035 IU/mL
Last AB-729 dose in Cohort K was at Week 40
*N=6; [#]N=5, 2 subjects did not receive Week 40 dose and were excluded from future timepoints

Figure 1: Change in HBsAg and HBeAg vs Time



Note: Dashed vertical lines indicate an AB-729 dosing visit; Two subjects (arrows, light blue and brown lines) did not receive the last dose (Week 40); HBsAg LLOQ = 0.07 IU/mL, <LLOQ defined as 0.035 IU/mL; HBeAg LLOQ = 0.11 IU/mL, <LLOQ defined as 0.055 IU/mL

- HBsAg:
  - All subjects in Cohort K had HBsAg <100 IU/mL during AB-729 treatment or follow up
  - Two subjects reached HBsAg <LLOQ with detectable HBsAb levels (5.08 – 11.18 mIU/mL)
- HBeAg:
  - The mean (SE) $\log_{10}$ change from baseline in HBeAg at Week 12 Post Last Dose was -0.93 (0.24) $\log_{10}$ IU/mL
  - One subject reached HBeAg <LLOQ intermittently, but no subjects had HBeAb seroconversion
- No subjects met protocol NA discontinuation criteria (all had residual detectable HBeAg)
- No safety events have been noted during the follow up period

RESULTS: NA DISCONTINUATION

Table 3: Baseline Characteristics

Baseline Measure	Pre-Study HBV DNA- (NA Suppressed)					Pre-Study HBV DNA+			
	Subject 46	Subject 52	Subject 51	Subject 53	Subject 61	Subject 56	Subject 59	Subject 58	Subject 60
Age (years)	35	36	49	61	56	52	36	50	46
Gender	Female	Male	Male	Female	Female	Female	Male	Male	Female
Race	Asian	Asian	Black	Asian	Asian	Asian	Asian	Asian	Asian
Study Cohort	E	F	F	F	I	G	G	G	G
NA therapy at study entry	ETV	TDF	ETV	TDF	ETV	none	none	none	none
Total duration of NA therapy	9 y, 7 m	17 y	6 y, 2 m	7 y, 5 m	6 y, 5 m	1 y, 6 m	1 y, 6 m	1 y, 6 m	1 y, 6 m

Note: All subjects who discontinued NAs were HBeAg negative at study entry

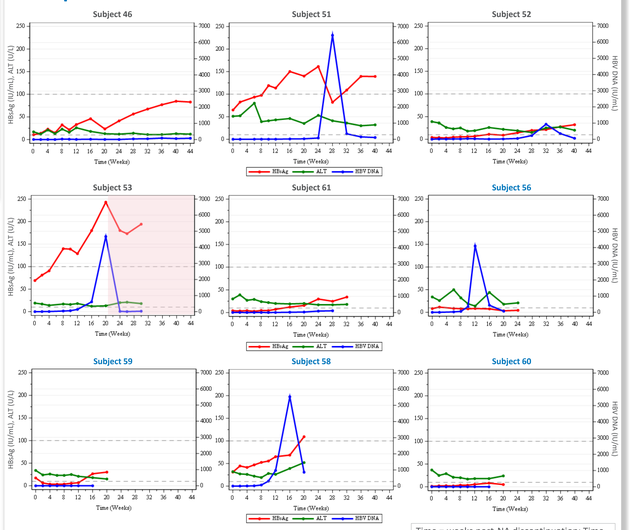
Table 4: HBV Markers

HBV Parameter	Pre-Study HBV DNA- (NA Suppressed)					Pre-Study HBV DNA+			
	Subject 46	Subject 52	Subject 51	Subject 53	Subject 61	Subject 56	Subject 59	Subject 58	Subject 60
HBV DNA (IU/mL)									
Study Day 1	TND	TND	TND	TND	TND	212,490	560	5840	9990
On trt Week 48	TND	<LLOQ	TND	TND	<LLOQ†	<LLOQ	TND	30	TND
Pre-NA d/c*	<LLOQ	<LLOQ	TND	TND	<LLOQ	<LLOQ	TND	<LLOQ	<LLOQ
NA d/c FU W4	<LLOQ	10	N/A[#]	10	TND	N/A[#]	TND	10	TND
NA d/c FU W12	10	30	<LLOQ	140	<LLOQ	4100	TND	970	<LLOQ
NA d/c FU W24	<LLOQ	50	80	*20‡*	90	-	-	-	-
NA d/c FU W36	90	350	150	-	-	-	-	-	-
Last available	80	60	110	*30‡*	110	70	TND	860	TND
HBsAg (IU/mL)									
Study Day 1	1392	1888	6765	2368	2021	277	1338	1397	1128
On trt Week 48	5.00	9.54	29.61	22.76	1.64†	6.61	1.46	15.15	0.51
Pre-NA d/c*	10.53	3.95	64.9	69.06	3.99	8.40	13.78	31.09	1.38
NA d/c FU W4	23.04	2.93	N/A[#]	90.69	4.18	N/A[#]	3.63	41.29	2.47
NA d/c FU W12	33.12	6.61	113.5	128.7	7.16	8.56	6.78	65.06	5.45
NA d/c FU W24	41.22	14.43	161.2	*180.1‡*	29.79	4.53	-	-	-
NA d/c FU W36	76.99	27.29	139.3	-	-	-	-	-	-
Last available	82.89	32.13	139.2	*194.2‡*	34.21	4.53	30.26	109.2	5.03

*Last timepoint prior to NA d/c (>24 weeks after last AB-729 dose); †Week 44 (Week 48 missed due to COVID-19); [#]missed visits due to COVID-19; [‡]post-NA restart; trt = treatment; d/c = discontinuation

- Subject 53 restarted NA therapy at Investigator's request after the NA d/c FU Week 20 visit (HBV DNA = 4,670 IU/mL), no ALT elevation or safety signals were observed
- No subjects have met protocol-defined criteria to restart NA therapy or had evidence of clinical/biochemical relapse (confirmed HBV DNA >2000 IU/mL plus ALT ≥ 2 × ULN)

Figure 2: Individual subject plots of HBV DNA, HBsAg and ALT post-NA discontinuation



Time = weeks post-NA discontinuation; Time 0 is at least 24 weeks post-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 of 100 IU/mL and 10 IU/mL

- Subject numbers in gray are pre-study HBV DNA- and in blue are pre-study HBV DNA+
  - Subject 53 restarted NA therapy after NA d/c Week 20 (time after NA restart is shaded pink)
- HBV DNA has transiently increased in 3 subjects and then spontaneously decreased without intervention (no NA therapy was given), suggesting host immune control
- Changes in HBV DNA do not appear to correlate with changes in HBsAg
- Subjects who were not on NAs at study entry do not appear more likely to relapse faster than NA suppressed subjects on NAs for 6 years or more prior to study entry
- The NA administered (ETV, TDF, or TAF) does not appear to impact post-NA discontinuation HBV viral parameters in this small dataset
- No ALT flares have been observed in any NA discontinuation subject

CONCLUSIONS

- AB-729 provided robust and sustained HBsAg declines in a cohort of HBeAg+ subjects, demonstrating a consistent treatment response with AB-729 regardless of HBeAg status.
  - Two subjects in Cohort K have achieved HBsAg below the limit of quantitation at multiple visits
  - No subjects met NA discontinuation criteria due to persistent low level HBeAg
- Discontinuation of NA therapy for up to 44 weeks in HBeAg- subjects who achieved HBsAg <100 IU/mL has been safe and well-tolerated to date, with no ALT flares observed.
- No evidence of clinical/biochemical relapse has been detected in the 9 subjects who have discontinued NA therapy with at least 12 - 44 weeks of follow up data available.
  - One subject restarted NA therapy per Investigator request (did not meet protocol-defined restart criteria)
  - Subjects who remain off NA therapy will continue to be followed for 3 years to monitor for sustained viral response and functional cure
- Subjects who have remained off NA therapy have maintained low HBV DNA and HBsAg levels for up to 44 weeks (68 weeks post-last AB-729 dose), suggestive of new viral set points via immune control.
  - HBsAg remains at least -1.05 $\log_{10}$ to -2.35 $\log_{10}$ below pre-study levels
  - Transient HBV DNA elevations in 3 subjects that spontaneously resolved further support potential for host immunological control
- These data support the continued evaluation of AB-729 as the cornerstone of combination treatment to achieve functional cure of chronic HBV.

REFERENCES

[1]European Association for the Study of the Liver, EASL 2017 Clinical Practice Guidelines on the management of hepatitis B infection. J Hepatol, 2017. 67(2):370-398.
[2]Sarin SK, et al. Hepatol Int, 2016. 10(1):1-98.
[3]Terrault N, et al. Hepatol, 2018. 67(4):1560-1599.
[4]Yuen MF, et al. AASLD 2020, #83.
[5]Gane E, et al. EASL 2021, #PO2879.
[6]Yuen MF, et al EASL 2022, #SAT443.
[7]Yuen MF, et al EASL 2022, #SAT448.

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