Preliminary safety and antiviral activity of AB-729 combination treatment with pegylated interferon alfa-2a in virally suppressed, HBeAg-negative subjects with chronic HBV infection

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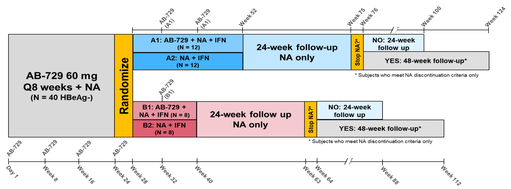
BACKGROUND

- Current therapies for chronic hepatitis B (CHB) including nucleos(t)ide analogues [NA] or pegylated interferon alfa-2a [IFN] slow or prevent the development of HBV-related liver complications, but do not typically lead to functional cure.[1,2,3]
- Excess production of HBsAg is believed to contribute to host immune exhaustion, resulting in inadequate T-cell and B-cell responses to CHB infection and failure to suppress the virus[4]. By targeting HBsAg and other viral antigen production in addition to suppressing viral replication, the anti-HBV host immune response may be restored.
- 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 leads to mean HBsAg declines of 1.8 to 2.6 $\log_{10}$ from baseline after 48 weeks of treatment[5], and preliminary data suggests that HBV-specific T cell responses may be enhanced following repeat dosing of AB-729[6].
- Given the immunostimulatory and HBsAg-lowering effects of Peg-IFNα-2a, a short pulse of Peg-IFNα-2a therapy in the context of profound suppression of HBsAg and viral replication by AB-729+NA may promote immune re-awakening and potentially lead to functional cure.
- AB-729-201 is a randomized, open-label, multicenter Phase 2a study assessing the safety, tolerability and antiviral activity of 24 weeks of AB-729 60 mg every 8 weeks followed by 12 or 24 weeks of pegylated interferon alfa-2a (IFN) with or without additional AB-729 doses in virally suppressed, HBeAg-negative CHB subjects. Here we report interim data through 12 weeks of IFN treatment for the first 12 subjects.

MATERIALS AND METHODS

AB-729-201 Study Design



- Study AB-729-201 enrolled 43 non-cirrhotic, HBeAg-negative, virally suppressed CHB subjects on stable NA therapy for at least 12 months prior to Day 1
- All subjects received 24 weeks (4 doses) of AB-729 60 mg every 8 weeks (Q8W) and were randomized at Week 24 into one of 4 groups (stratified by HBsAg level at Week 24 ≤100 or >100 IU/mL):
  - A1: AB-729 + NA + weekly Peg-IFNα-2a for 24 weeks (N = 12 planned)
  - A2: NA + weekly Peg-IFNα-2a for 24 weeks (N = 12 planned)
  - B1: AB-729 + NA + weekly Peg-IFNα-2a for 12 weeks (N = 8 planned)
  - B2: NA + weekly Peg-IFNα-2a for 12 weeks (N = 8 planned)
- After completion of the IFN treatment period, subjects were followed for an additional 24 weeks on NA alone, then assessed for NA discontinuation via the following criteria:
  - ALT <2× ULN, undetectable HBV DNA, and HBsAg <100 IU/mL at two consecutive visits at least 24 weeks after the last dose of AB-729
- Key inclusion/exclusion criteria:

Inclusion:
- Males and females 18-60 years of age
- HBsAg between 100 – 5,000 IU/mL
- HBV DNA < lower limit of quantitation (LLOQ)
- Fibroscan ≤8.5 kPa within 6 months of Day 1

Exclusion:
- Coinfection with HDV, HIV or HCV
- ALT > 2× upper limit of normal (ULN)
- Direct or total bilirubin > 1.5× ULN
- Neutrophils <1500 cells/mm^3, platelets <150,000 cells/mm^3

- Study assay methods/cutoffs:
  - HBsAg was assessed with Roche Cobas Elecsys, LLOQ = 0.05 IU/mL
  - HBV DNA was assessed with Roche Cobas 6800, LLOQ = 10 IU/mL
  - ALT upper limit of normal (ULN) = 41 U/L for males, 33 U/L for females

RESULTS

Table 1: Demographic and Baseline Characteristics

Category	Cohort A1 AB-729+NA+IFN 24 wks (N=11)	Cohort A2 NA + IFN 24 wks (N=13)	Cohort B1 AB-729+NA+IFN 12 wks (N=7)	Cohort B2 NA + IFN 12 wks (N=10)	Total (N=43)*
Age, mean (SD)	44.6 (7.24)	41.5 (6.05)	47.6 (4.08)	47.2 (4.21)	45.3 (6.36)
Males, n (%)	5 (45.5)	12 (92.3)	6 (85.7)	6 (85.7)	31 (72.1)
Race					
Asian	9 (81.8)	9 (69.2)	6 (85.7)	8 (80.0)	34 (79.1)
White	2 (18.2)	3 (23.1)	0	2 (20.0)	7 (16.3)
Other	0	1 (7.7)	1 (14.3)	0	2 (4.6)
HBsAg, mean (SD) $\log_{10}$ IU/mL	2.99 (0.46)	2.91 (0.52)	2.98 (0.35)	3.06 (0.59)	2.98 (0.48)
ALT mean (SD), U/L	19.09 (6.36)	25.31 (9.81)	26.43 (9.25)	25.80 (10.99)	24.58 (10.33)

*2 subjects not yet randomized to an IFN group; NA: nucleos(t)ide analogue; IFN: pegylated interferon alfa-2a; wks: weeks; ALT: alanine aminotransferase

- Baseline characteristics were similar across treatment cohorts, with slightly more females in Cohort A1

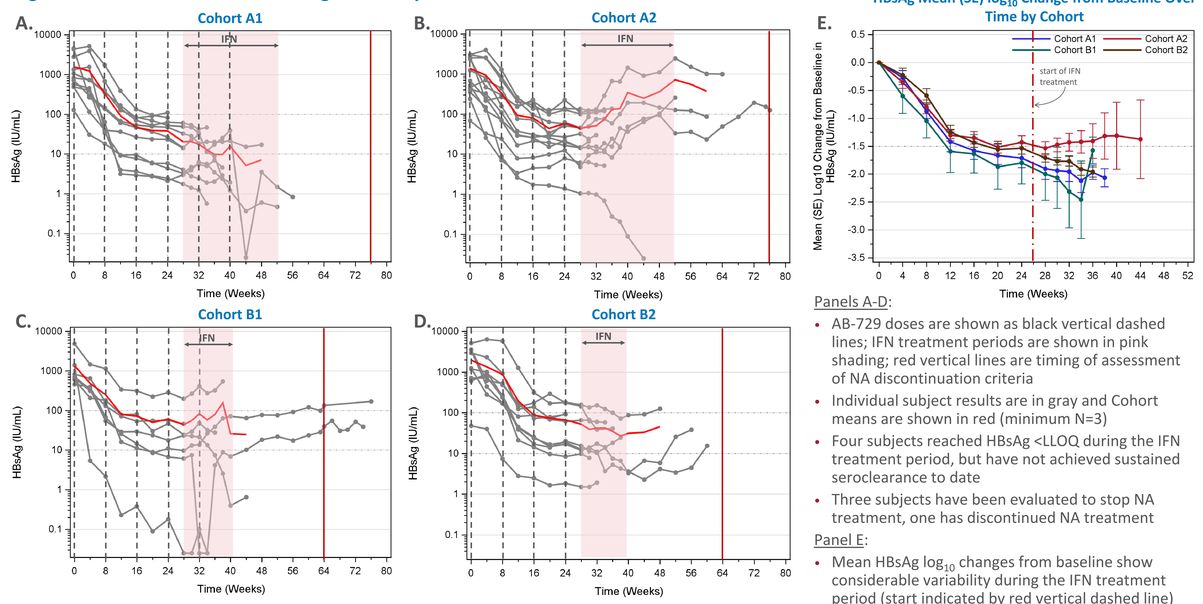
Table 2: Mean (SE) HBsAg $\log_{10}$ Change from Baseline at Key Timepoints

Timepoint	Cohort A1 AB-729+NA+IFN 24 wks N	Cohort A1 AB-729+NA+IFN 24 wks Mean (SE)	Cohort A2 NA + IFN 24 wks N	Cohort A2 NA + IFN 24 wks Mean (SE)	Cohort B1 AB-729+NA+IFN 12 wks N	Cohort B1 AB-729+NA+IFN 12 wks Mean (SE)	Cohort B2 NA + IFN 12 wks N	Cohort B2 NA + IFN 12 wks Mean (SE)	Total N	Total Mean (SE)
Baseline level	11	2.99 (0.14)	13	2.91 (0.14)	7	2.98 (0.13)	10	3.06 (0.19)	43	2.98 (0.07)
Δ at Week 12	11	-1.42 (0.18)	13	-1.30 (0.10)	7	-1.59 (0.38)	10	-1.25 (0.12)	43	-1.37 (0.09)
Δ at Week 24	11	-1.71 (0.17)	13	-1.43 (0.12)	7	-1.80 (0.37)	10	-1.54 (0.10)	42	-1.59 (0.09)
Δ at Week 40 (12 weeks IFN*)	4	-2.22 (0.28)	5	-1.31 (0.60)	3	-2.04 (0.71)	3	-2.20 (0.23)	15	-1.88 (0.26)
Δ at Week 52 (24 weeks IFN#)	2	-3.36 (0.12)	4	-0.56 (0.27)	2	-1.17 (0.40)	2	-1.99 (0.33)	10	-1.53 (0.37)

*All Cohorts; #Cohorts A1 and A2 only; NA: nucleos(t)ide analogue; IFN: pegylated interferon alfa-2a; wks: weeks; SE: standard error

- AB-729 treatment led to a mean 1.59 $\log_{10}$ decline from baseline by Week 24
- On-treatment mean HBsAg declines at Week 40 (week 12 of IFN dosing) are promising but sample sizes remain small

Figure 1: Individual and Mean HBsAg Results by Cohort Over Time



HBsAg LLOQ = 0.05 IU/mL

Panels A-D:
- AB-729 doses are shown as black vertical dashed lines; IFN treatment periods are shown in pink shading; red vertical lines are timing of assessment of NA discontinuation criteria
- Individual subject results are in gray and Cohort means are shown in red (minimum N=3)
- Four subjects reached HBsAg <LLOQ during the IFN treatment period, but have not achieved sustained seroclearance to date
- Three subjects have been evaluated to stop NA treatment, one has discontinued NA treatment

Panel E:
- Mean HBsAg $\log_{10}$ changes from baseline show considerable variability during the IFN treatment period (start indicated by red vertical dashed line) but remain below baseline values

Table 3: On-Treatment Safety

Subjects, n (%)	Study Treatment Period: AB-729 Lead-In (N=43)	Cohort A1 AB-729+NA+IFN 24 wks (N=11)	Cohort A2 NA + IFN 24 wks (N=13)	Cohort B1 AB-729+NA+IFN 12 wks (N=7)	Cohort B2 NA + IFN 12 wks (N=10)	Study Total (N=43)*
Any TEAE	21 (48.8%)	5 (45.5%)	6 (46.2%)	5 (71.4%)	5 (50.0%)	29 (67.4%)
Grade 1	14 (32.6%)	1 (9.1%)	3 (23.1%)	4 (57.1%)	3 (30.0%)	14 (32.6%)
Grade 2	4 (9.3%)	4 (36.4%)	2 (15.4%)	1 (14.3%)	1 (10.0%)	10 (23.3%)
Grade 3	3 (7.0%)	0	1 (7.7%)	0	1 (10.0%)	5 (11.6%)
Grade 4	0	0	0	0	0	0
Treatment-related TEAEs						
AB-729	9 (20.9%)	0	N/A	0	N/A	9 (20.9%)
IFN	N/A	4 (36.4%)	4 (30.8%)	3 (42.9%)	4 (40.0%)	15 (34.9%)
SAEs	0	0	0	0	0	0
Study discontinuation due to TEAEs	0	0	0	0	0	0

*2 subjects not yet randomized to an IFN group NA: nucleos(t)ide analogue; IFN: pegylated interferon alfa-2a; wks: weeks; TEAE: treatment emergent adverse event; SAE: serious adverse event

- AB-729 with or without IFN was generally well-tolerated, with most TEAEs assessed as unrelated to AB-729
  - AB-729-related TEAEs were all Grade 1 except for 1 Grade 2 headache and 2 Grade 3 ALT elevations that improved during continued AB-729 treatment
- There were no SAEs, study discontinuations or AB-729 treatment discontinuations/modifications
- 5 subjects required IFN dose modifications or interruptions due to IFN-related laboratory abnormalities (neutropenia in 4, ALT elevation in 1)
- 3 Grade 4 laboratory abnormalities were observed
  - CK elevation due to strenuous exercise and dietary supplements
  - 2 Grade 4 low neutrophils during IFN treatment (Cohorts A2 and B2, without AB-729)

CONCLUSIONS

- AB-729 60 mg every 8 weeks added to ongoing NA therapy led to mean HBsAg declines of 1.6 $\log_{10}$ at week 24 of treatment, comparable to other AB-729 studies
  - HBsAg levels < 100 IU/mL were noted during the treatment period in 93% of subjects
- 4 subjects reached HBsAg <LLOQ during IFN treatment, but sustained seroclearance has not been observed to date in this limited sample size
- AB-729 treatment alone or in combination with IFN was generally well tolerated in this larger dataset
  - IFN-related TEAEs were consistent with the known safety profile
  - 5 subjects required IFN dose modifications due to laboratory abnormalities
- This interim data analysis suggests addition of IFN to AB-729 treatment was well tolerated and may result in continued HBsAg declines in some subjects
- Additional follow-up is needed to determine if the addition of IFN is beneficial at the end of the treatment period and during follow-up, and if continuation of AB-729 dosing during IFN treatment promotes continued HBsAg decline
- This study remains ongoing with most subjects still in the early IFN treatment period; subjects will continue to be followed for on-treatment responses and eligibility to discontinue NA therapy during the follow-up period

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