AB-729, a GalNAc-siRNA, results in robust reductions of HBV DNA and HBsAg in subjects with chronic hepatitis B infection

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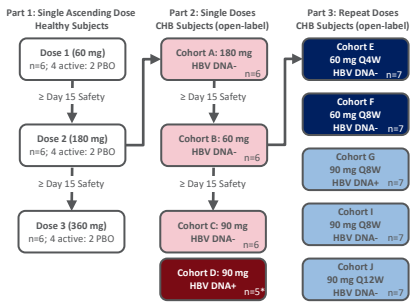
BACKGROUND

- Chronic hepatitis B (CHB) can result in the development of cirrhosis, hepatocellular carcinoma, and progression to end-stage liver disease.[1,2]
- Current therapies slow or prevent the development of HBV-related liver complications,[3,4,5] but do not typically lead to a cure. Thus, there is an unmet medical need for new HBV therapies that have the potential to provide a functional cure for CHB.
- AB-729 is a subcutaneously administered single trigger GalNAc-conjugated RNA interference therapeutic candidate. The proprietary GalNAc liver targeting technology ensures high affinity and uptake into hepatocytes via the asialoglycoprotein receptor (ASGPr).
- In preclinical models, AB-729 reduced all HBV transcripts and antigens thereby inhibiting HBV replication,[6] and was shown to have activity against all HBV genotypes in vitro.
- AB-729-001 is a 3-part study examining the safety and pharmacodynamics (PD) of AB-729 (Figure 1).
  - Single doses of AB-729 (Cohorts A, B, C) and repeat dosing of AB-729 60 mg every 4 weeks (Q4W, Cohort E) in virologically-suppressed CHB subjects have been previously reported.[7]
- Here we report safety and PD through:
  - 24 weeks following a single dose of AB-729 90 mg in HBV DNA+ CHB subjects, in the absence of nucleos(t)ide analogue (NA) therapy (**Cohort D**)
  - 24 weeks with repeat dosing of AB-729 60 mg every 4 weeks (Q4W) in virologically-suppressed subjects (**Cohort E**)
  - 16 weeks with repeat dosing of AB-729 60 mg every 8 weeks (Q8W) in virologically-suppressed subjects (**Cohort F**).

AB-729-001 STUDY DESIGN

Figure 1. AB-729-001 Study Design

In Part 2, AB-729 was administered to subjects as single doses of 60 mg – 180 mg on Day 1. In Part 3, repeat doses of AB-729 60 mg or 90 mg were administered at varying dosing intervals for 20 weeks.



Q4W: every 4 weeks, Q8W: every 8 weeks; Q12W: every 12 weeks
*One subject removed from analysis due to spontaneous HBV flare prior to dosing (pre-dose Day 1 ALT elevated to 149 U/L from Screening value of 24 U/L, TDF initiated by investigator on Day 8), thus data presented are for N=5

Key Inclusion Criteria:

- All Cohorts: HBeAg positive or negative; HBsAg ≥ 250 IU/mL
- Virologically-suppressed Cohorts (A, B, C, E, F, I, J): HBV DNA < LLOQ, on stable NA treatment for ≥ 6 months
- HBV DNA+ Cohorts (D, G): HBV DNA ≥ 1000 IU/mL
- Single dose Cohorts (A, B, C, D): ALT/AST ≤ 5xULN
- Repeat dose Cohorts (E, F, G, I, J): ALT/AST ≤ 2xULN

RESULTS

Table 1. Baseline Characteristics

Baseline Measure	Cohort D 90 mg SD HBV DNA+ [N=5]	Cohort E 60 mg Q4W [N=7]	Cohort F 60 mg Q8W [N=7]
Age in years, mean (range)	43.6 (35 – 57)	45.1 (33 – 63)	44.0 (31 – 59)
Male gender, n (%)	3 (60%)	4 (57%)	4 (57%)
BMI mean (SD)	29.2 (5.42)	27.7 (5.01)	23.7 (2.17)
Race, n (%)			
Asian	0	1 (14%)	5 (71%)
White	4 (80%)	6 (86%)	1 (14%)
Black	0	0	1 (14%)
Other	1 (20%)	0	0
ALT (U/L) mean (SD)	31.6 (13.4)	22.4 (10.5)	23.4 (15.2)
HBV eAg-, n (%)	5 (100%)	7 (100%)	6 (86%)
HBsAg (IU/mL) mean (range)	2336 (317 – 6,451)	5372 (584 – 11,761)	5354 (667 – 18,605)
HBV DNA (IU/mL) mean (range)	86,840 (1,220 – 360,560)	N/A	N/A

SD: single dose

RESULTS

Figure 2: Individual and mean change from baseline HBsAg (A) and HBV DNA (B) following a single dose of AB-729 90 mg in HBV DNA+ subjects (Cohort D)

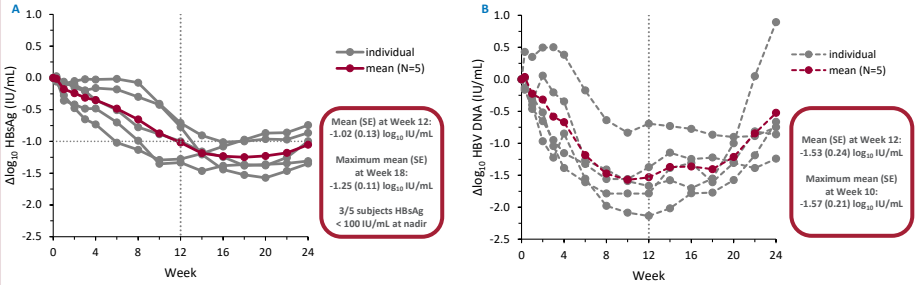
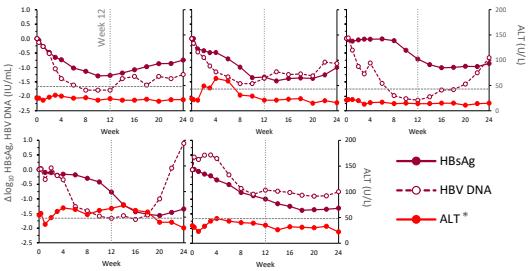
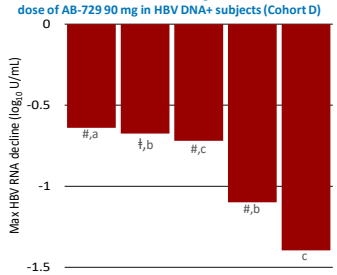


Figure 3: Individual HBsAg, HBV DNA, and ALT following administration of a single dose of AB-729 90 mg in HBV DNA+ subjects (Cohort D)



*dotted horizontal line represents ALT ULN (43 U/L for females, 48 U/L for males)

Figure 4: Individual maximum HBV RNA decline within the first 12 weeks following administration of a single dose of AB-729 90 mg in HBV DNA+ subjects (Cohort D)



HBV RNA samples below the lower the limit of quantitation (1.65 log_{10} U/mL, ǂ) or target not detected (#) assigned a value of 1.64 log_{10} U/mL for the purpose of this assessment.
Last available HBV RNA timepoint at Week 12 (a), Week 8 (b), and Week 10 (c)

Figure 5: Mean (SE) Δlog_{10} HBsAg following repeat dosing of AB-729 60 mg Q4W (Cohort E) and Q8W (Cohort F)

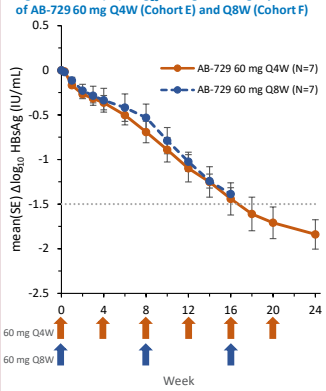


Table 2. Safety Results

Subjects, n (%)	Cohort D (90 mg SD HBV DNA+) [N=5]	Cohort E (60 mg Q4W) [N=7]	Cohort F (60 mg Q8W) [N=7]	TOTAL [N=19]
Subjects with any TEAE	3 (60)	4 (57)	4 (57)	11 (58)
Subjects with related TEAEs (all Grade 1)	1 (20)	2 (29)	4 (57)	7 (37)
Most common related TEAEs (in ≥ 2 subjects):				
Injection site pain	0	0	2 (29)	2 (3)[a]
Injection site erythema	0	2 (29)	1 (14)	4 (6)[a]
Injection site bruising	1 (20)	2 (29)	0	3 (4)[a]
Laboratory Abnormalities (in ≥ 2 subjects):				
ALT elevation				
Grade 1	2 (40)	2 (29)	1 (14)	5 (26)
Grade 2‡	0	2 (29)	1 (14)[†]	3 (16)
AST elevation (Gr 1)	0	2 (29)	2 (29)	4 (21)
Sodium (low, Gr 1)	0	1 (14)	1 (14)	2 (11)

TEAE: treatment-emergent adverse event
Grading criteria based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1
[a]n, % is number of events out of 70 total AB-729 doses administered
‡Grade 2 ALT elevations were transient and all improved to Grade 1
†Subject had history of pre-study Grade 1 ALT abnormalities

Table 3. Summary PD data for AB-729 60 mg administered every 4 weeks or every 8 weeks

Visit	AB-729 60 mg Q4W [Cohort E, N=7]		AB-729 60 mg Q8W [Cohort F, N=7]	
Week 16	Mean (SE) Δlog_{10} HBsAg: **-1.44 (0.18) IU/mL**	4/7 HBsAg < 100 IU/mL 4/7 > 1.5 log_{10} HBsAg decline	Mean (SE) Δlog_{10} HBsAg: **-1.39 (0.07) IU/mL**	3/7 HBsAg < 100 IU/mL 3/7 > 1.5 log10 HBsAg decline
Week 24	Mean (SE) Δlog_{10} HBsAg: **-1.84 (0.16) IU/mL**	5/7 HBsAg < 100 IU/mL 6/7 > 1.5 log_{10} HBsAg decline	not yet available	

CONCLUSIONS

- **In HBV DNA+ CHB subjects administered a single dose of AB-729 90 mg in the absence of NA therapy:**
  - HBsAg remained suppressed in all subjects up to 24 weeks post-dose; however HBV DNA rebound was observed in some subjects post-Week 12.
  - HBV RNA declined in all subjects up to 12 weeks post-dose (the last time point available for HBV RNA), with 4/5 subjects reaching either undetectable or unquantifiable HBV RNA at some point.
  - ALT elevations were benign and did not appear to correlate with either HBsAg or HBV DNA profiles, including HBV DNA rebound.
  - These data continue to support AB-729 dosing in combination with other agents at intervals up to every 12 weeks.
- **In virologically suppressed CHB subjects administered AB-729 60 mg every 4 weeks (Cohort E) or every 8 weeks (Cohort F):**
  - Mean (SE) HBsAg declines were similar up to Week 16, providing further evidence that AB-729 can be dosed less frequently than every 4 weeks.
  - Mean HBsAg continued to decline through Week 24 following repeat dosing of AB-729 60 mg every 4 weeks.
    - 7/7 subjects have consented to participate in a treatment extension arm where they will continue to receive AB-729 for an additional 6 months.
    - Based on single dose PD data presented previously,[7] the dosing interval of AB-729 60 mg was increased to every 12 weeks for the extension period.
- **AB-729 was well tolerated after single doses in HBV DNA+ subjects and after multiple doses in virologically suppressed CHB subjects:**
  - All TEAEs were Grade 1 excepting one case of unrelated COVID-19 with fever (Grade 2).
  - Transaminase elevations were modest and transient, none were symptomatic or were accompanied by bilirubin elevations or other clinically relevant laboratory changes and were not assessed as TEAEs.

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