A single dose of the GalNAc-siRNA AB-729 results in prolonged reductions in HBsAg, HBcrAg, HBV DNA and HBV RNA in the absence of nucleos(t)ide analogue therapy in HBeAg- subjects with chronic hepatitis B infection

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Arbutus BIOPHARMA Curing Chronic Hepatitis B

INTRODUCTION

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 *N*-Acetylgalactosamine (GalNAc)-conjugated single trigger RNA interference therapeutic that blocks all HBV RNA transcripts, including HBx, resulting in suppression of viral replication and all viral antigens.[6] AB-729 is currently in Phase 2a development for the treatment of CHB in combination with other agents.

AIM

Here we report safety and PD up to 48 weeks following a single dose (SD) of AB-729 90 mg in HBV DNA+ CHB subjects, in the absence of nucleos(t)ide analogue (NA) therapy.

METHODS

AB-729-001 is a 3-part study examining the safety and pharmacodynamics (PD) of AB-729. Safety and PD following single doses of AB-729 (Part 2 Cohort A, B, C) in virologically-suppressed CHB subjects on (NA) therapy have been reported previously.[7,8]

In Part 2 Cohort D, HBV DNA+ CHB subjects [N=6] either off therapy for 6 months or naïve to treatment received a single dose of AB-729 90 mg in the absence of a NA with follow-up for 48 weeks post-dose. These subjects were HBeAg positive or negative, with HBsAg ≥ 250 IU/mL, HBV DNA ≥ 1,000 IU/mL, and ALT/AST ≤ 5xULN at screening.

RESULTS

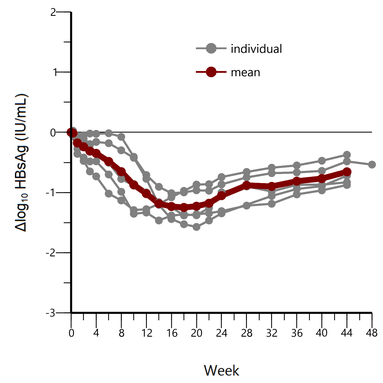
One subject was removed from analysis due to spontaneous HBV flare prior to dosing (pre-dose Day 1 ALT elevated to 149 U/L from Screening value of 24 U/L, TDF initiated by investigator on Day 8), thus data presented are for N=5. No other subjects initiated NA during the follow-up period.

Table 1. Baseline characteristics (N=5)

Age in years, mean (range)	43.6 (35 – 57)
Male gender, n (%)	3 (60%)
BMI, mean (SD)	29.2 (5.42)
Race	
White	4 (80%)
Other	1 (20%)
ALT (U/L), mean (SD)	31.6 (13.4)
HBV eAg negative, n (%)	5 (100%)
HBsAg (IU/mL), mean (range)	2,336 (317 – 6,451)
HBV DNA (IU/mL), mean (range)	86,840 (1,220 – 360,560)

RESULTS

Figure 1. Individual and mean change from baseline HBsAg following a single dose of AB-729 90 mg in HBV DNA+ subjects



Week 12 Mean (SE) : -1.02 (0.13)

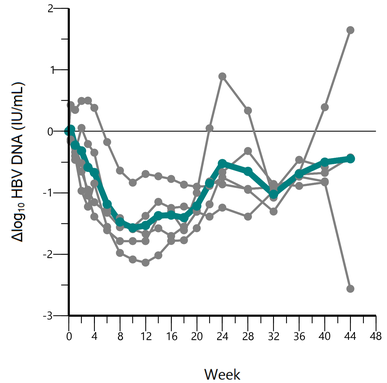
Week 24 Mean (SE): -1.05 (0.12)

Week 36 Mean (SE): -0.812 (0.09)

Week 44 Mean (SE): -0.657 (0.10)

3/5 subjects HBsAg < 100 IU/mL at nadir

Figure 2. Individual and mean change from baseline HBV DNA following a single dose of AB-729 90 mg in HBV DNA+ subjects

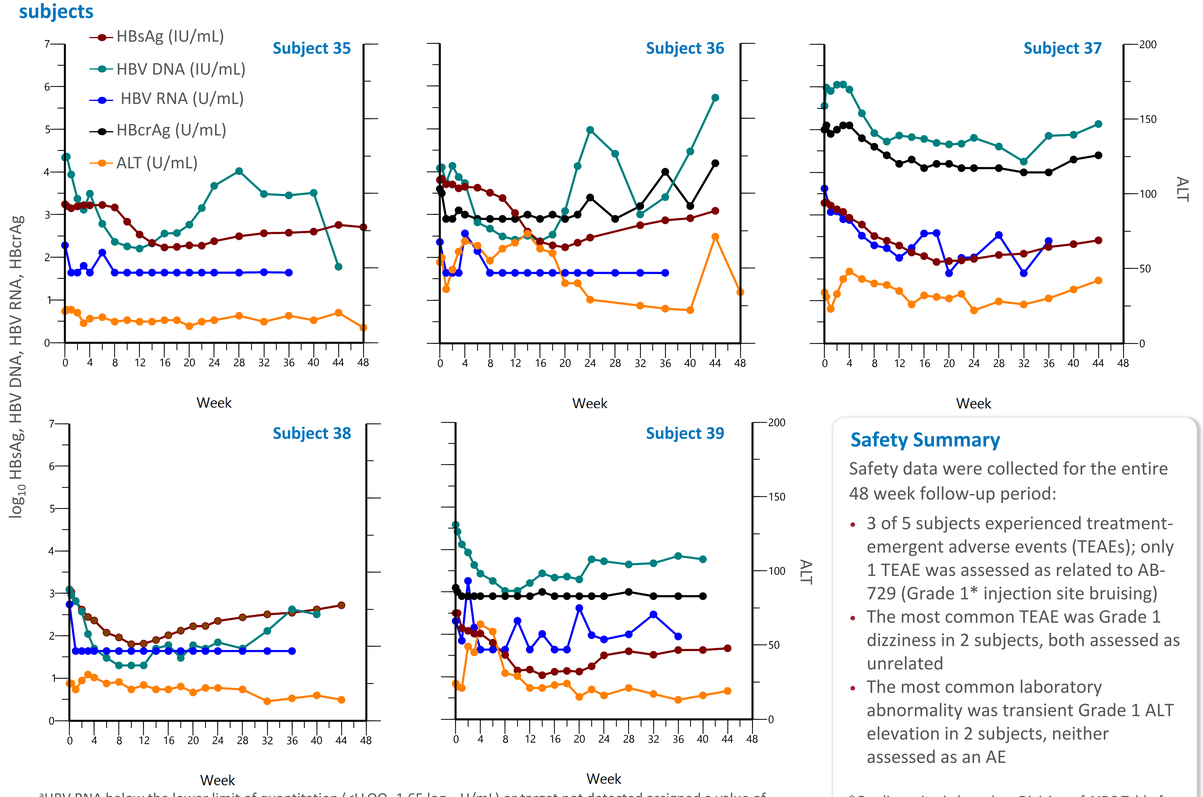


Week 12 Mean (SE) : -1.53 (0.24)

Week 24 Mean (SE): -0.525 (0.37)

Week 36 Mean (SE): -0.693 (0.07)

Figure 3. Individual HBsAg, HBV DNA, HBV RNA,[a] HBcrAg,[b,c] and ALT following a single dose of AB-729 90 mg in HBV DNA+ subjects



[a]HBV RNA below the lower limit of quantitation (<LLOQ, 1.65 log_{10} U/mL) or target not detected assigned a value of 1.64 log_{10} U/mL.
[b]HBcrAg <LLOQ (3.0 log_{10} U/mL) assigned a value of 2.9 log_{10} U/mL.
[c]Baseline HBcrAg <LLOQ in subjects 35 and 38.

Safety Summary

Safety data were collected for the entire 48 week follow-up period:

- 3 of 5 subjects experienced treatment-emergent adverse events (TEAEs); only 1 TEAE was assessed as related to AB-729 (Grade 1* injection site bruising)
- The most common TEAE was Grade 1 dizziness in 2 subjects, both assessed as unrelated
- The most common laboratory abnormality was transient Grade 1 ALT elevation in 2 subjects, neither assessed as an AE

*Grading criteria based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1

CONCLUSIONS

- In HBV DNA+ CHB subjects, a single dose of AB-729 90 mg in the absence of NA therapy achieved potent and durable antiviral responses.
  - HBsAg concentrations remained below baseline levels in all subjects up to 48 weeks post-dose.
  - HBV DNA concentrations remained below baseline levels in 4/5 subjects up to 44 weeks post-dose.
    - The exception was subject #36 with notably fluctuating HBV DNA levels post Week 22.
    - No subject initiated NA during the follow-up period.
  - Rebounds in HBV DNA did not correlate with HBsAg or ALT elevations.
    - The exception was subject #36; however ALT levels did not appreciably exceed baseline levels at any point post-dose
  - All subjects had quantifiable HBV RNA at baseline:
    - Max HBV RNA declines of -0.64 to -1.98 log_{10} U/mL were observed.
    - 5/5 subjects reached undetectable/unquantifiable HBV RNA levels post-dose.
  - In subjects with quantifiable HBcrAg at baseline (3/5 subjects),
    - Max declines of -0.2 to -1.0 log_{10} U/mL were observed.
    - 2/3 subjects reached unquantifiable levels of HBcrAg post-dose.
  - AB-729 was well-tolerated in this cohort of HBV DNA+ subjects
- These single dose data demonstrate full target engagement by AB-729, as evidenced by declines in HBsAg, HBV DNA, HBV RNA, and HBcrAg.

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