Inhibition of hepatitis B surface antigen by RNA interference therapeutic AB-729 is associated with increased cytokine signatures in HBV DNA+ chronic hepatitis B subjects

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INTRODUCTION

Therapeutic strategies aimed at reducing antigenemia, particularly hepatitis B surface antigen (HBsAg), may trigger HBV-specific immune restoration in chronic hepatitis B (CHB).

AB-729 is a subcutaneously administered single trigger GalNAc-conjugated RNA interference therapeutic candidate, currently in Phase 2 development for the treatment of CHB in combination with other agents.

Figure 1.
AB-729 is a single siRNA trigger RNAi therapeutic that targets all HBV RNA, leading to reduction of HBV antigens including HBsAg

OBJECTIVE

- To compare the effect of a single AB-729 administration on cytokine/chemokine expression in CHB subjects who are undergoing nucleos(t)ide analog (NA) therapy (HBV DNA-) with those who are not on NA treatment (HBV DNA+)

BACKGROUND

- AB-729-001 is a three part, Ph1a/b clinical study
- Longitudinal plasma samples from CHB subjects receiving a single injection of AB-729 (90 mg) who are HBV DNA- (n=6) and HBV DNA+ (n=5) were assessed for cytokines/chemokines using multiplex Luminex assays. Analyses presented here are based on samples collected up to 14 weeks post-AB-729 single dose administration.

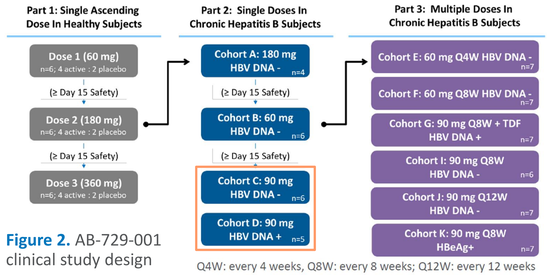


Figure 2. AB-729-001 clinical study design

Key inclusion criteria:

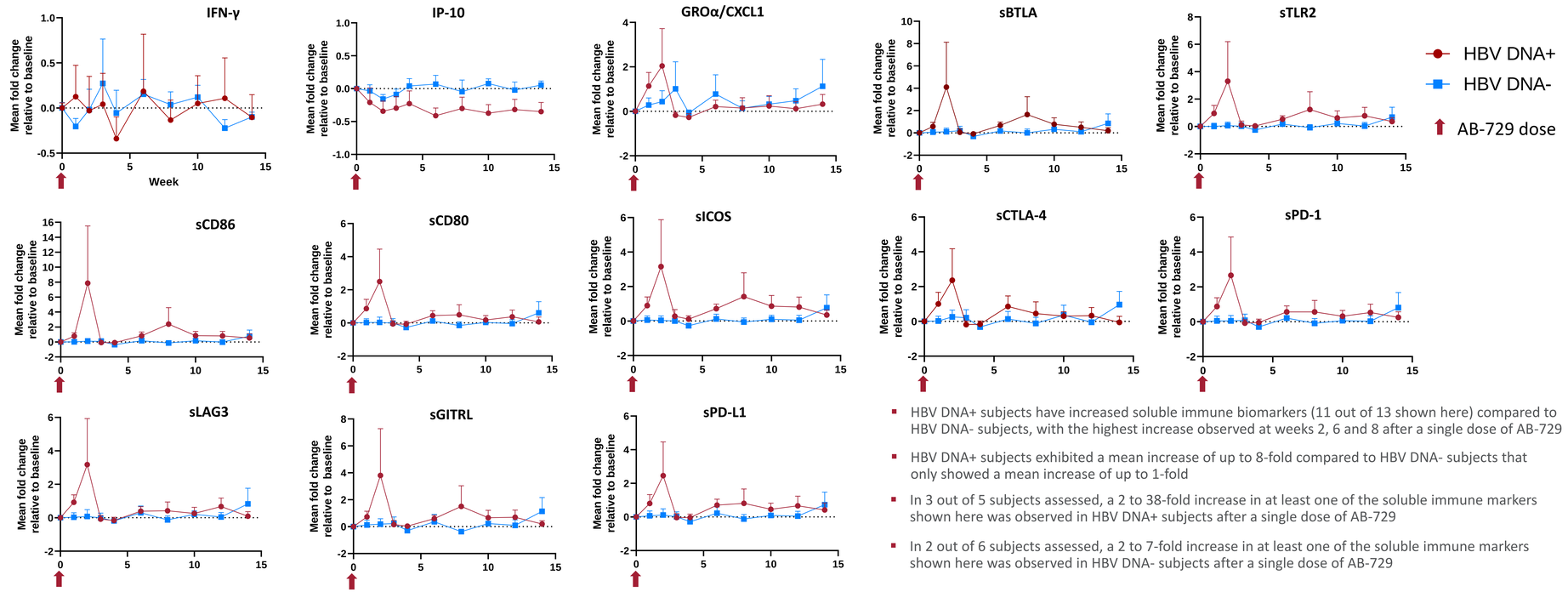
Cohorts A to J: HBeAg positive or negative; HBsAg ≥ 250 IU/mL

Cohort K: HBeAg positive; HBsAg ≥ 250 IU/mL

- Virologically-suppressed Cohorts (A, B, C, E, F, I, J, K): HBV DNA < LLOQ, on stable nucleos(t)ide analogue 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, K): ALT/AST ≤ 2xULN

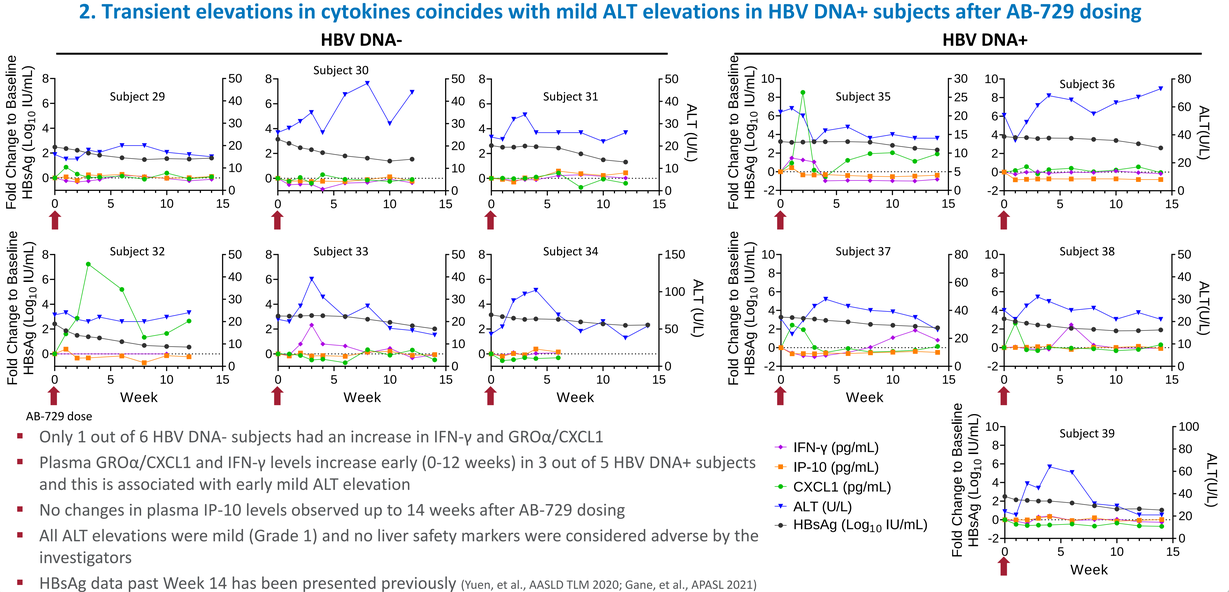
RESULTS

1. Greater breadth of soluble immune biomarkers are increased in HBV DNA+ compared to HBV DNA- subjects after a single dose of AB-729



- HBV DNA+ subjects have increased soluble immune biomarkers (11 out of 13 shown here) compared to HBV DNA- subjects, with the highest increase observed at weeks 2, 6 and 8 after a single dose of AB-729
- HBV DNA+ subjects exhibited a mean increase of up to 8-fold compared to HBV DNA- subjects that only showed a mean increase of up to 1-fold
- In 3 out of 5 subjects assessed, a 2 to 38-fold increase in at least one of the soluble immune markers shown here was observed in HBV DNA+ subjects after a single dose of AB-729
- In 2 out of 6 subjects assessed, a 2 to 7-fold increase in at least one of the soluble immune markers shown here was observed in HBV DNA- subjects after a single dose of AB-729

2. Transient elevations in cytokines coincides with mild ALT elevations in HBV DNA+ subjects after AB-729 dosing



- Only 1 out of 6 HBV DNA- subjects had an increase in IFN-γ and GROα/CXCL1
- Plasma GROα/CXCL1 and IFN-γ levels increase early (0-12 weeks) in 3 out of 5 HBV DNA+ subjects and this is associated with early mild ALT elevation
- No changes in plasma IP-10 levels observed up to 14 weeks after AB-729 dosing
- All ALT elevations were mild (Grade 1) and no liver safety markers were considered adverse by the investigators
- HBsAg data past Week 14 has been presented previously (Yuen, et al., AASLD TLM 2020; Gane, et al., APASL 2021)

CONCLUSIONS

- Greater breadth of soluble immune biomarker responses with T cell activation signatures observed in HBV DNA+ subjects compared to NA-suppressed HBV DNA- subjects
- Our study suggests HBV DNA+ subjects are more immunologically responsive following AB-729 dosing
- This represents the first data comparing immunological responses of HBV DNA+ and HBV DNA- CHB subjects undergoing HBsAg reduction following GalNAc-siRNA treatment
- Assessment of responses following AB-729 repeat dosing in HBV DNA+ subjects with concomitant initiation of NA therapy is ongoing

METHODS

Soluble immune biomarkers were assessed using multiplex Luminex assays

CONTACT

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