Inhibition of Hepatitis B Surface Antigen in Chronic Hepatitis B Subjects by RNA Interference Therapeutic AB-729 is Accompanied by Upregulation of HBV-Specific T-Cell Activation Markers

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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 2a 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

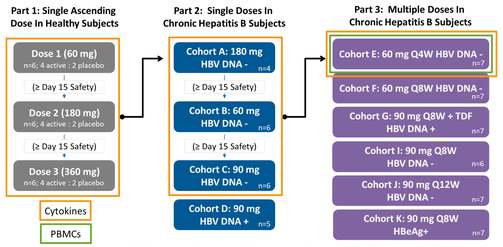
OBJECTIVES

- To characterize the effect of AB-729 administration on cytokine/chemokine expression in healthy subjects and CHB patients
- To assess the effect of prolonged AB-729-mediated HBsAg suppression on HBV-specific T-cell activation markers

BACKGROUND

- AB-729-001 is a three part, Ph1a/b clinical study
- Longitudinal plasma samples from healthy subjects and CHB patients receiving a single injection of AB-729 (60-360 mg, n=10 or 16) were assessed for cytokines/chemokines using multiplex Luminex assays
- Longitudinal plasma or peripheral blood mononuclear cell samples from patients (n=6 or 5) undergoing repeat dosing of 60 mg AB-729 every 4 weeks (Q4W) for 6 doses were assessed using Luminex, interferon gamma (IFN-γ) T-cell fluorospot and T-cell proliferation assay

Figure 2.
AB-729-001 clinical study design



Q4W: every 4 weeks, Q8W: every 8 weeks; Q12W: every 12 weeks

Key inclusion criteria:

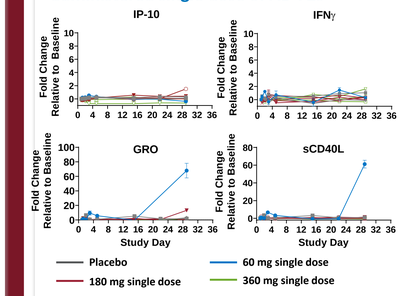
Cohorts A to J: HBeAg positive or negative; HBsAg ≥ 250 IU/mL

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 (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, K): ALT/AST ≤ 2xULN

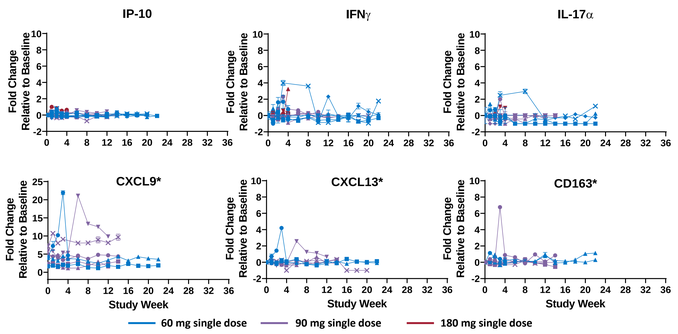
RESULTS

Figure 3. No meaningful increases in most cytokines observed in healthy subjects administered single dose of AB-729



Healthy subjects received a single dose of AB-729 (60 mg, 180 mg or 360 mg) or placebo.
No significant increases were observed compared to pre-dose baseline levels for 64 out of 66 cytokines and soluble immune markers tested.
One subject in 60 mg single dose cohort had elevated GRO and sCD40L at 28 days post-dose which was not associated with clinical changes or changes in other cytokines or soluble immune markers tested.
N=10 out of 18 subjects who provided consent.

Figure 4. Transient elevations in plasma IFN-γ, IL-17a, CXCL9, CXCL13 and CD163 observed in CHB patients following single dose of AB-729

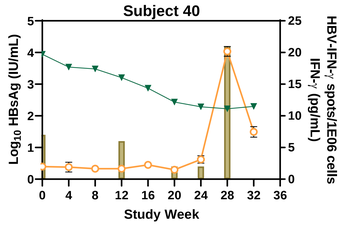


CHB NA-suppressed patients received a single dose of AB-729 (60 mg, 90 mg or 180 mg). Transient elevations of 2 to 6-fold over pre-dose baseline levels for IFN-γ, IL-17a, CXCL9, CXCL13 and CD163 were observed for N=3 out of 6 patients for each analyte.

Data are means ± SEM of technical duplicate or triplicate samples for each timepoint for each patient.
Shown are 6 cytokines for which meaningful changes were observed out of 44 cytokines assessed.
N=16 out of 16 patients with the exception of CXCL9, CXCL13 and CD163 assessments.
*Data not yet available for 180 mg single dose cohort, and 3 out of 6 patients in 60 mg single dose cohort

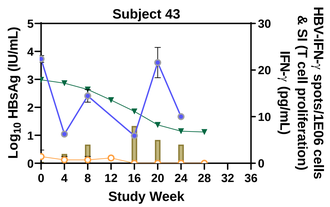
Figure 5. HBsAg reduction in CHB patients undergoing AB-729 60 mg Q4W repeat dosing is accompanied by upregulation of HBV-specific T cell activation markers

A Elevated plasma IFN-γ observed in one patient undergoing AB-729 Q4W repeat dosing



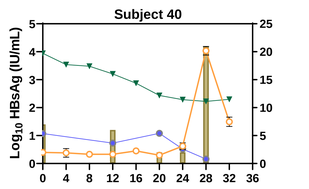
In Subject 40, a 1.7 $\log_{10}$ reduction in HBsAg preceded a 9-fold elevation in plasma IFN-γ at Week 28, which coincided with an increase in IFN-γ-producing HBV-specific T-cells.

Small Change HBV T-cell IFN-γ
No Change HBV T-cell Proliferation

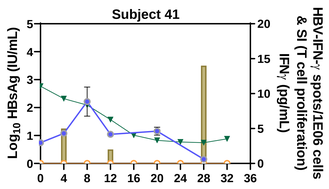


B 3 out of 5 subjects show increases in HBV-specific T-cell proliferation or HBV-specific T-cell IFN-γ production

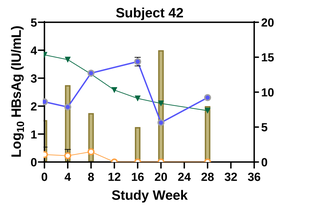
↑ HBV T-cell IFN-γ



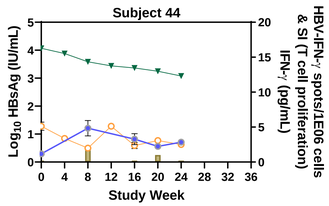
↑ HBV T-cell IFN-γ
↑ HBV T-cell Proliferation



↑ HBV T-cell IFN-γ
↑ HBV T-cell Proliferation



↑ HBV T-cell Proliferation



Elevated HBV-specific T-cell proliferation was observed by Week 8 for Subjects 41, 42, 44 (considered elevated if S.I. ≥ 3.0 and ≥2-fold change relative to baseline stimulation index).

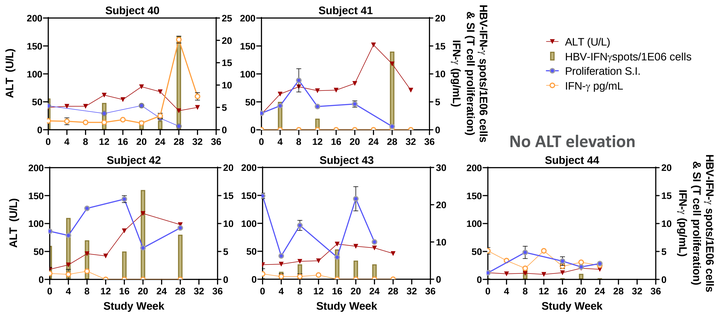
Increases in IFN-γ-producing HBV-specific T-cells coincided with ≥1.7 $\log_{10}$ HBsAg reduction in Subjects 40, 41, 42.

PBMC samples available from 5 out of 7 subjects
S.I. = Stimulation index upon HBV peptides stimulation, calculated as mean counts per minute in HBV peptides stimulated wells divided by the mean counts per minute in control wells
A positive response is defined as an index of 3.0 or higher (Ref. 2)

Figure 6. Mild to moderate ALT elevations preceded or coincided with IFN-γ-producing HBV-specific T-cells

ALT elevation precedes

ALT elevation coincides



Mild to moderate ALT elevations observed in NA-suppressed CHB patients undergoing AB-729 repeat dosing at 60 mg Q4W, which was associated with HBV-specific T-cell IFN-γ production.

- 2/5 patients ALT elevation classified as Grade 1 (Ref. 3)
- 2/5 patients ALT elevation classified as Grade 2 (Ref. 3)

No changes were observed in any patients for inflammatory cytokine IP-10 or other liver safety markers. None of these ALT elevations were considered adverse events by the Investigators.

CONCLUSIONS

- AB-729-mediated HBsAg reduction is associated with increased HBV-specific immune responses in a subset of CHB patients
  - These increases in HBV-specific immune responses are accompanied by mild to moderate ALT elevations
- To our knowledge, the present study is the first to demonstrate reawakening of HBV-specific immune responses following long-term HBsAg suppression with siRNA therapy
- These results suggest effects of AB-729 therapy may be enhanced by combination with immunomodulatory agents

REFERENCES

1. Yuen MF, et al. Safety and pharmacodynamics of the GalNAc-siRNA AB-729 in subjects with chronic hepatitis B infection. Presented at the Liver Meeting Digital Experience, November 15, 2020.
2. Park J, et al. Hepatitis B Virus–Specific and Global T-Cell Dysfunction in Chronic Hepatitis B. Gastroenterology. 2016; 150: 684-695.
3. European Association for the Study of the Liver, EASL 2017 Clinical Practice Guidelines on the management of hepatitis B infection. Journal of Hepatology. 2017; 67(2):370-398.

METHODS

- Cytokines/chemokines were assessed using multiplex Luminex assays
- Peripheral blood mononuclear cell samples from subjects were stimulated with HBV overlapping peptides against core and HBsAg or medium control and assessed for:
  - HBV-specific T-cell IFN-γ production by IFN-γ T-cell fluorospot assay
  - HBV-specific T-cell proliferation by measuring ^{3}H-thymidine incorporation

CONTACT

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