Reduction of hepatitis B surface antigen mediated by RNA interference therapeutic AB-729 in chronic hepatitis B patients is associated with T cell activation and a decline in exhausted CD8 T cells

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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.

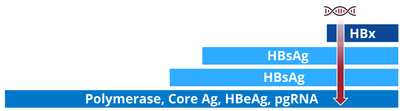


Figure 1.
AB-729 is a single siRNA trigger RNAi therapeutic that targets all HBV RNA, leading to reduction of HBV antigens including HBsAg.

OBJECTIVES

- To characterize effect of AB-729 administration on the cytokine/chemokine profile and T cell activation of CHB subjects
- ➢ Data are extended beyond Week 32[1] to include up to 16 weeks follow-up post AB-729 treatment

BACKGROUND

- AB-729-001 is a three part, Ph1a/b clinical study
- Longitudinal plasma samples from CHB subjects receiving repeat dosing of AB-729 every 4 weeks (60 mg Q4W up to Week 24, then changed to every 12 weeks thereafter to Wk 40 in extension phase, n=6) and every 8 weeks (60 mg Q8W, n=7) were assessed for cytokines/chemokines using multiplex assays
- Longitudinal peripheral blood mononuclear cell (PBMCs) samples were available from a subset of CHB subjects receiving repeat dosing of AB-729 every 4 weeks (n=5) and every 8 weeks (n=2). PBMCs were assessed using interferon gamma (IFN-γ) T-cell fluorospot and T cell proliferation assay

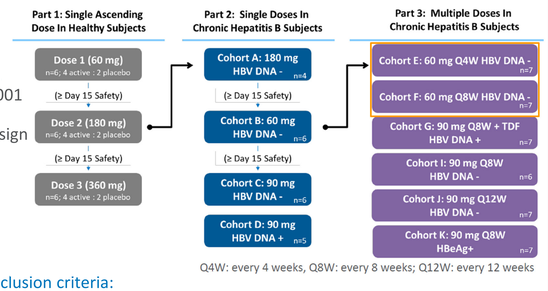


Figure 2.
AB-729-001 clinical study design

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

Key inclusion criteria:

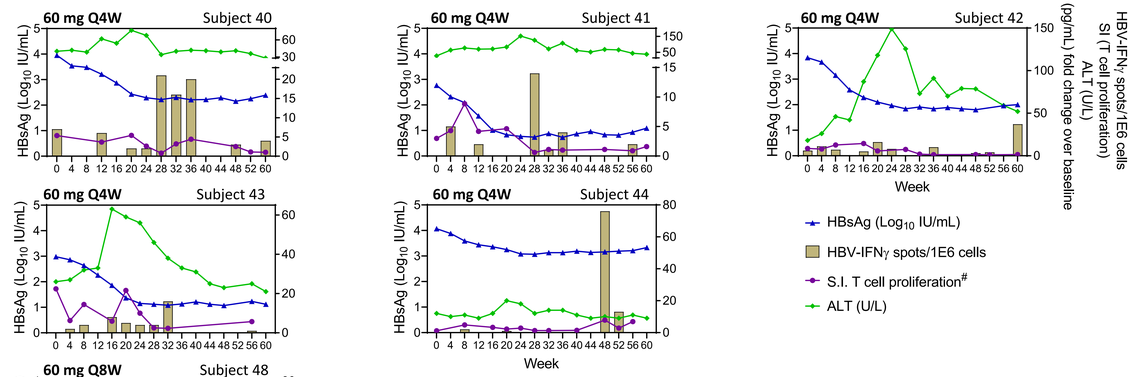
Cohorts A to J: HBeAg positive or negative; HBsAg ≥ 250 IU/mL

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
- Repeat dose Cohorts (E, F, G, I, J, K): ALT/AST ≤ 2xULN[2]

RESULTS

1. HBV-specific T cell activation markers are upregulated in CHB subjects undergoing AB-729 repeat dosing



A Upregulation of HBV-specific T cell activation markers observed in all 7 subjects assessed to date with available PBMC samples
- ➢ 5/5 subjects in AB-729 60 mg Q4W cohort
- ➢ 2/2 subjects in AB-729 60 mg Q8W cohort

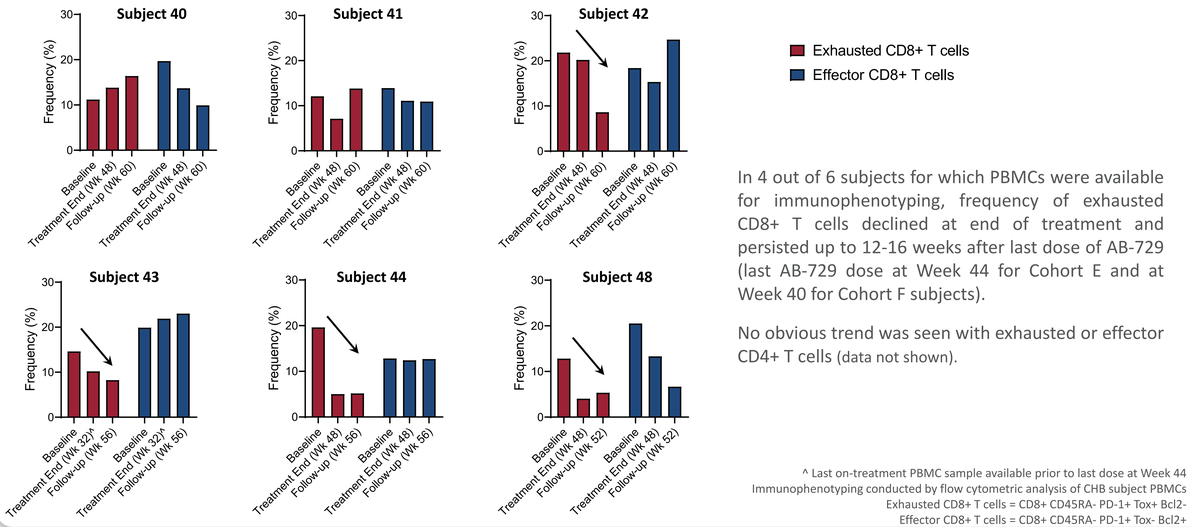
B Two profiles of HBV-specific T cell IFN-γ responses observed
- ➢ Elevation between Week 16-28 which coincides with nadir of HBsAg reduction (Subjects 40, 41, 43, 48, 53)
- ➢ Elevation after AB-729 dosing is complete, between Week 48-60 (Subjects 42, 44)

Cytokine assessment of IFN-γ in plasma did not reveal appreciable increase in plasma IFN-γ for 6 out of 7 subjects. A transient 9-fold elevation in IFN-γ was observed for Subject 40 at Week 28.

C In some instances, mild to moderate ALT elevations observed in NA-suppressed CHB subjects undergoing AB-729 repeat dosing are associated with HBV-specific T-cell IFN-γ production. None of these ALT elevations were considered adverse events by the Investigators.

Proliferation 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. 3)

2. AB-729 treatment resulted in a decline of CD8+ exhausted T cells, which persisted 12-16 weeks after completing AB-729 treatment



In 4 out of 6 subjects for which PBMCs were available for immunophenotyping, frequency of exhausted CD8+ T cells declined at end of treatment and persisted up to 12-16 weeks after last dose of AB-729 (last AB-729 dose at Week 44 for Cohort E and at Week 40 for Cohort F subjects).

No obvious trend was seen with exhausted or effector CD4+ T cells (data not shown).

^ Last on-treatment PBMC sample available prior to last dose at Week 44
Immunophenotyping conducted by flow cytometric analysis of CHB subject PBMCs
Exhausted CD8+ T cells = CD8+ CD45RA- PD-1+ Tox+ Bcl2-
Effector CD8+ T cells = CD8+ CD45RA- PD-1+ Tox- Bcl2+

3. HBV-specific T cell activation profiles and clinical outcomes

To date, HBV T cell activation markers have been profiled in 7 CHB subjects through Week 32 to 60. Assessment of additional subjects is on-going.

- One subject seroconverted and HBsAg became <LLOQ at Week 84; 40 weeks after last dose of AB-729 and beyond current HBV T cell data set (see Yuen, et al., Poster # SAT443)
- One subject met pre-defined nucleos(t)ide analog (NA) treatment discontinuation criteria and elected to stop NA treatment (see Yuen, et al., Poster # SAT448)
  - ➢ 5 subjects did not meet NA discontinuation criteria

Subject ID	Cohort	HBV T cell IFN-γ Increase	HBV T cell Proliferation	HBsAg at Baseline (IU/mL)	Lowest HBsAg between 24-48 weeks after AB-729 (IU/mL)
40	60 mg Q4W	Wk 28-36	Wk 0-20, 36	8816	606.2
41	60 mg Q4W	Wk 28	Wk 4-20	583.5	<LLOQ
42	60 mg Q4W	Wk 60	Wk 0-28	6853	168.2
43	60 mg Q4W	Wk 32	Wk 0-24, 56	964.5	20.01
44	60 mg Q4W	Wk 48-52	Wk 48, 56	11761	2719
48	60 mg Q8W	Wk 36	No	3338	200.2
53	60 mg Q8W	Wk 24-28	No	2368	46.11

CONCLUSIONS

- AB-729-mediated HBsAg reduction is associated with increased HBV-specific T cell activation and proliferation from baseline in CHB subjects
- A decline in exhausted CD8+ T cells at end of treatment and at 12-16 weeks of follow-up suggest that HBV-specific T cell immune reawakening may be durable
- The limited data thus far suggests that an increase in HBV-specific T cell activation at the nadir of HBsAg reduction may be beneficial to clinical outcomes; however, profiling greater numbers of subjects with different outcomes is warranted
- Results suggest effects of AB-729 treatment may be enhanced by combination with immunomodulatory agents

REFERENCES

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4. Boni C, et al. Poster 833. The Liver Meeting Digital Experience, November 12-15, 2020.

METHODS

- Cytokines/chemokines were assessed using multiplex Luminex assays
- PBMCs 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 and HBV-specific T-cell proliferation by ^{3}H-thymidine incorporation
- Exhausted and effector CD4+ and CD8+ T cells were assessed by PBMC immunophenotyping. Exhausted T cells were gated as PD-1+ Tox+ Bcl2- and Effector T cells were gated as PD-1+ Tox- Bcl2+, as defined in Ref. 4.

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