Inhibition of Hepatitis B Surface Antigen by RNA Interference Therapeutic AB-729 in Chronic Hepatitis B Patients Correlates with Suppression of All HBsAg Isoforms and HBV RNA

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Poster Session Online

INTRODUCTION

AB-729 is a subcutaneously administered single trigger GalNAc-conjugated RNA interference therapeutic candidate.

In preclinical models, AB-729 reduced all HBV transcripts and antigens thereby inhibiting HBV replication, and was shown to have activity against all HBV genotypes *in vitro.*

AB-729 is 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, including HBsAg mRNA and the viral replicative intermediate, pgRNA

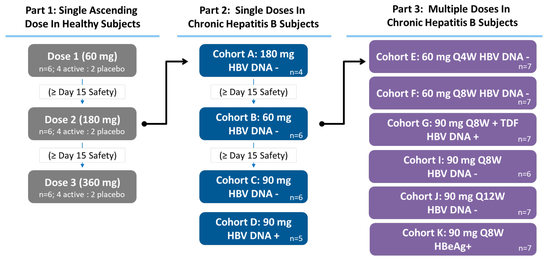
OBJECTIVES

- Determine the effect of AB-729 on the novel HBV biomarkers HBV RNA, HBsAg isoforms and HBsAg immune complex
- Assess degree of correlation of these novel markers with AB-729 effects on total HBsAg and HBV DNA

BACKGROUND

- AB-729-001 is a three part, Phase 1a/b clinical study
- Data presented are from longitudinal plasma samples from CHB subjects undergoing AB-729 dosing in Part 2 (single dose, 60-180 mg, n=22) or Part 3 (repeat dosing at 60 mg every 4 weeks for 6 doses, n=7; or 60 mg every 8 weeks for 3 doses, n=7)

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

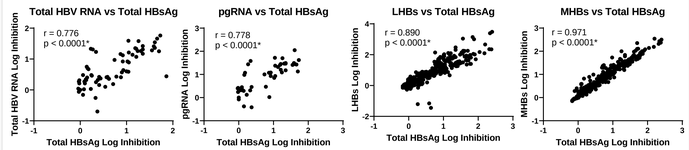
Cohort K: HBeAg positive; HBsAg ≥ 250 IU/mL

- 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

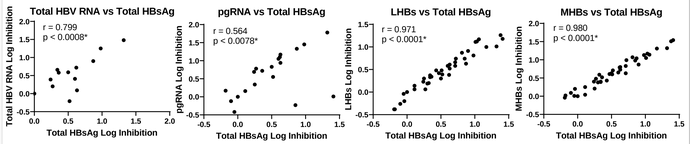
RESULTS

Figure 3. AB-729 mediated reductions in total HBsAg correlate with inhibition of HBV RNA and HBsAg isoforms

A AB-729 treated nucleos(t)ide-analogue suppressed CHB subjects



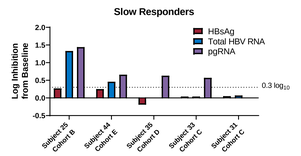
B AB-729 treated HBV DNA+ CHB subjects



Data are log_{10} reduction from baseline for timepoints up to Week 36
* Pearson correlation, two tailed
HBV RNA data only included if quantifiable

Figure 4. AB-729 reduces HBV RNA in both slow and fast HBsAg responders

A Slow Responders: HBV RNA inhibition at Day 29
Slow responder defined as <0.3 log_{10} reduction in HBsAg 4 weeks after AB-729 dose initiation



B Fast Responders: HBV RNA inhibition at Day 29
Fast responder defined as >0.3 log_{10} reduction in HBsAg 4 weeks after AB-729 dose initiation

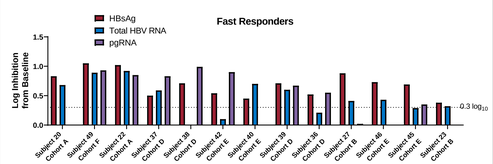
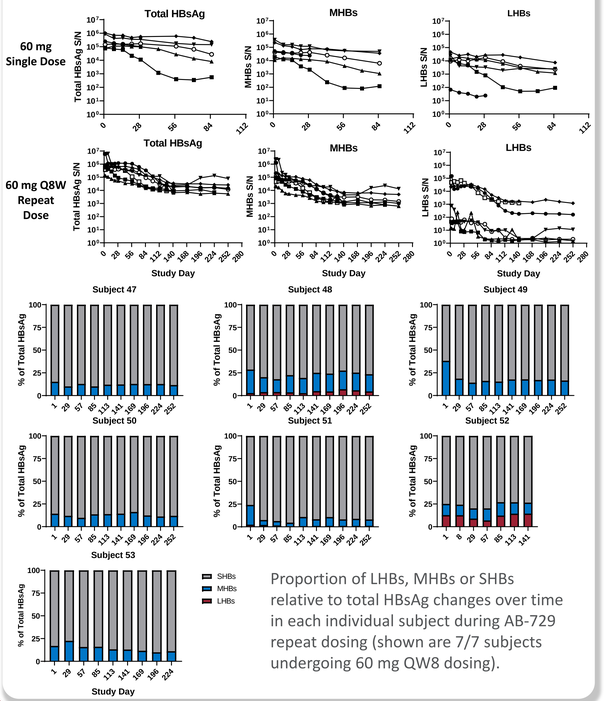


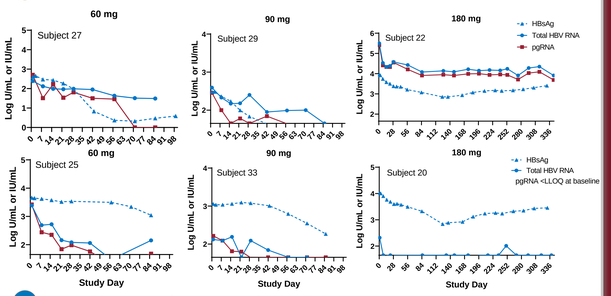
Figure 5. AB-729 reduction of Large (LHBs) and Middle (MHBs) HBsAg isoforms parallels total HBsAg inhibition



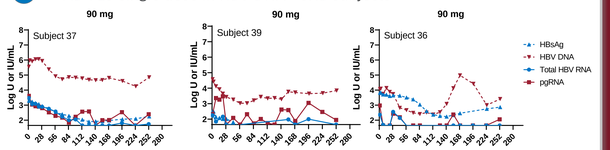
Proportion of LHBs, MHBs or SHBs relative to total HBsAg changes over time in each individual subject during AB-729 repeat dosing (shown are 7/7 subjects undergoing 60 mg QW8 dosing).

Figure 6. AB-729 reduction of HBV RNA species parallels HBsAg and HBV DNA inhibition

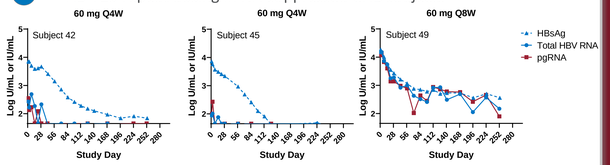
A AB-729 single dose in NA-suppressed CHB subjects



B AB-729 single dose in HBV DNA+ CHB subjects



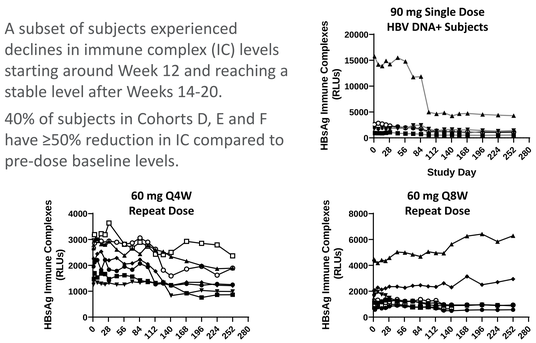
C AB-729 repeat dosing in NA-suppressed CHB subjects



Only subjects with quantifiable HBV RNA at baseline shown. HBV RNA values <LLOQ assigned a value of 1.65 log_{10} IU/mL; TND assigned a value of 1.64 log_{10} IU/mL

Figure 7. Changes in HBsAg immune complex levels in subset of subjects undergoing AB-729 dosing

- A subset of subjects experienced declines in immune complex (IC) levels starting around Week 12 and reaching a stable level after Weeks 14-20.
- 40% of subjects in Cohorts D, E and F have ≥50% reduction in IC compared to pre-dose baseline levels.



RLUs = Relative Luminescence Units

CONCLUSIONS

- AB-729 mediated total HBsAg decline correlated with decreases in circulating HBV RNA species and both HBsAg isoforms
- Early reduction in HBV RNA was observed in both "slow" and "fast" responders, confirming rapid target engagement by AB-729 in all CHB subjects
- A subset of subjects receiving AB-729 experience a consistent decline in HBsAg immune complex levels
- Additional profiling of other cohorts and timepoints may provide further insights into the relationship of these novel HBV biomarkers with the antiviral effect of AB-729

REFERENCES

1. Yuen MF, et al. Safety and pharmacodynamics of a GalNAc-siRNA AB-729 in subjects with chronic hepatitis B infection. Presented at the Liver Meeting Digital Experience, November 15, 2020.
2. Butler EK, et al. Hepatitis B Virus Serum DNA and RNA Levels in Nucleos(t)ide Analog-Treated or Untreated Patients During Chronic and Acute Infection. Hepatology. 2018; 68:2106-2121.
3. Rodgers MA, et al. HBV surface antigen large and middle isoform composition are proportional to total HBsAg. 2019; Poster 0675.

METHODS

- HBsAg was quantified using Roche cobas Elecsys HBsAg II quant II assay, with LOD = 0.05 IU/mL
- HBV DNA was quantified using Abbott RealTime HBV Viral Load assay, with LOD = 15 IU/mL
- HBV RNA was quantified using a Research Use Only dual-target real-time quantitative PCR on Abbott m2000 system (Abbott Diagnostics, Ref. 1). LOD = 1.65 log U/mL for total HBV RNA and 1.81 log U/mL for pgRNA.
- HBsAg isoforms were detected using Research Use Only chemiluminescent immunoassays (Abbott Diagnostics, Ref. 2). Assay cutoff = 2.4 S/N.
- HBsAg immune complex was quantitated using Research Use Only chemiluminescent immunoassay (Abbott Diagnostics)

CONTACT

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