A Phase 2a Study Evaluating the Multi-dose Activity of ARB-1467 in HBeAg-Positive and -Negative Virally Suppressed Subjects with Hepatitis B

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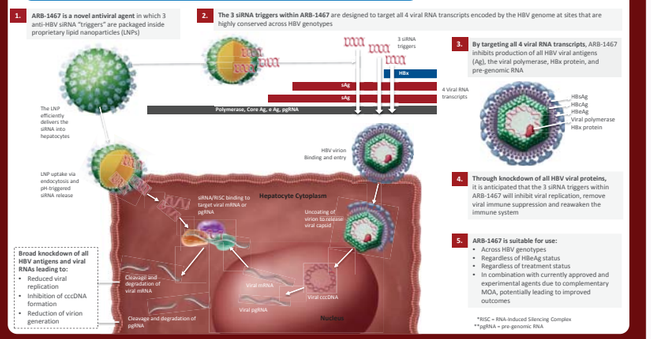
INTRODUCTION

ARB-1467 is a novel RNA interference (RNAi) product, containing the drug substance UsiHBV-1, consisting of three synthetic double-stranded, small interfering RNAs (siRNAs) directed against hepatitis B virus (HBV) messenger RNAs (mRNAs), targeting three distinct sites in the HBV genome. ARB-1467 is designed to inhibit viral replication, reduce all HBV transcripts, and lower all viral antigens. Reducing viral proteins, in particular hepatitis B surface antigen (HBsAg), has the potential to mitigate viral suppression and reawaken the immune system.

ARB-1467 MODE OF ACTION



STUDY DESIGN AND METHODS

Phase 2a Single-Blind Study in HBV Patients
Duration of treatment: 3-month follow-up, 12 months after the first dose

- HBeAg-Negative ARB-1467 0.2 mg/kg monthly n=8 (6 active, 2 placebo)
- HBeAg-Negative ARB-1467 0.4 mg/kg monthly n=8 (6 active, 2 placebo)
- HBeAg-Positive ARB-1467 0.4 mg/kg monthly n=8 (6 active, 2 placebo)
- HBeAg-Negative ARB-1467 0.4 mg/kg bi-weekly n=12 (12 active)

Key inclusion criteria:
- Adult subjects with CHB
- ALT ≤2X ULN, HBV-DNA <LLQ and FibroScan <12 kPa
- Receiving entecavir or tenofovir for at least 12 months

Dose administration:
- ARB-1467 injection (2 mg/mL) administered IV over 2 hours, monthly, for 3 months
- Pre-medications administered to mitigate infusion-related reactions
- Safety monitoring and HBV markers were performed at Days 2, 3, 8, 15, 22, 29, 30, 36, 43, 50, 57, 58, 64, 71, 83, 275 and 365

OBJECTIVES

Primary Objective

- To evaluate the safety and tolerability of multiple doses of ARB-1467 in subjects with hepatitis B virus e-antigen (HBeAg)-negative or HBeAg-positive chronic HBV infection who are receiving nucleos(t)ide analogue therapy

Secondary Objective

- To evaluate the antiviral activity of ARB-1467 for up to 72 weeks after the first dose of study treatment

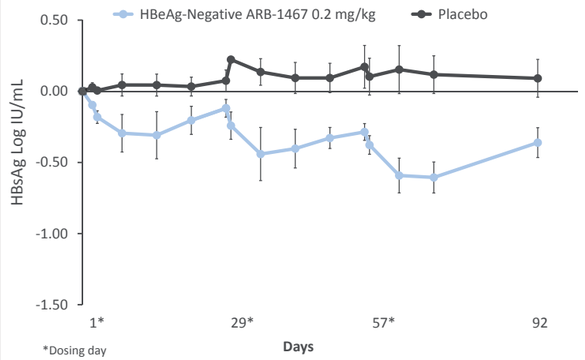
DEMOGRAPHICS

Baseline characteristics were similar among the three cohorts
- Gender: 19/24 (79%) were male
- Age: mean age was 45.5 years
- Race: 8/24 (33%) were Asian
- Mean HBsAg at baseline (log_{10} IU/mL): 3.46, 3.38, 3.62 and 3.43 in Cohorts 1, 2, 3 and placebo, respectively

RESULTS

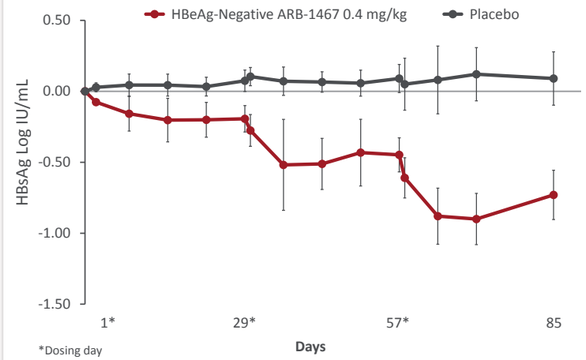
HBeAg-Negative (ARB-1467 0.2 mg/kg): Multiple-Dose Results

HBsAg Mean Log Change From Baseline



HBeAg-Negative (ARB-1467 0.4 mg/kg): Multiple-Dose Results

HBsAg Mean Log Change From Baseline

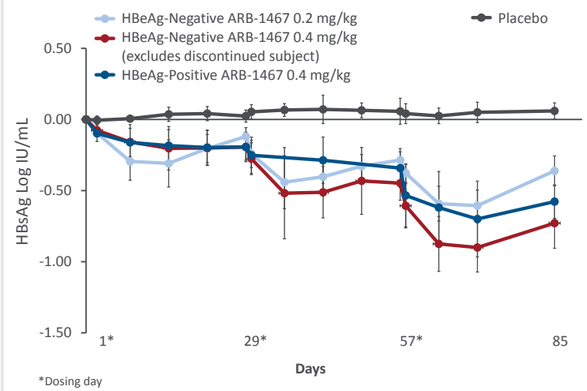


1 subject discontinued at Day 36 due to acute HEV super-infection – excluded from the multi-dose analysis.

HBeAg-Positive (ARB-1467 0.4 mg/kg): Multiple-Dose Results

HBsAg Mean Log Change From Baseline

Overall Summary



Single- and Multiple-Dose Serum HBsAg Reduction

Cohort	ARB-1467 (mg/kg)	HBeAg	Single-Dose HBsAg Reduction (log_{10} IU/mL)				Multiple-Dose HBsAg Reduction (log_{10} IU/mL)					
			N	Mean[a]	Mean Max[b]	Max[c]	N	Mean[a]	Mean Max[b]	Max[c]	>0.5 log[d]	>1.0 log[d]
1	0.2	Neg	6	-0.3	-0.4	-1.0	6	-0.6	-0.7	-1.3	5	1
2	0.4	Neg	6	-0.2	-0.3	-0.8	5*	-0.9	-1.0	-1.3	4	3
3	0.4	Pos	6	-0.2	-0.3	-0.6	6	-0.7	-0.8	-1.6	4	2
Placebo	N/A		6	0.0	0.0	-0.1	6	0.0	-0.1	-0.1	0.0	0.0

[a] The mean serum HBsAg reduction is the nadir value of the arithmetic mean of all values observed at each time point.
[b] The mean maximum HBsAg reduction is the mean of each patient's maximum reduction in serum HBsAg.
[c] Maximum HBsAg reduction is the best single reduction among all patients in a cohort.
[d] Proportion of subjects.
*1 subject discontinued at Day 36 due to acute hepatitis E virus (HEV) super-infection – excluded from the multi-dose analysis.

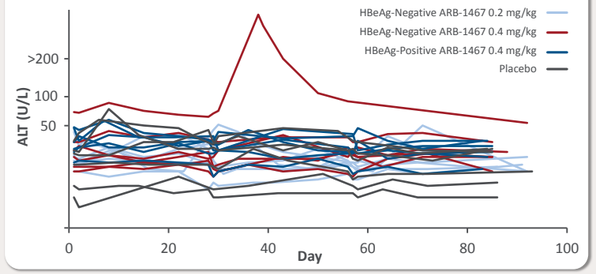
Overall Safety

Patients, N (%)	HBeAg-Negative ARB-1467 0.2 mg/kg n=6	HBeAg-Negative ARB-1467 0.4 mg/kg n=6	HBeAg-Positive ARB-1467 0.4 mg/kg n=6	Placebo n=6
Any AE	5 (83)	5 (83)	2 (33)	5 (83)
Grade 3-4 AE	1 (17)	0	0	0
Serious AE	1 (17)*	0	0	0
Discontinuation due to AE	0	1 (17)**	0	0
Grade 3 or 4 lab abnormalities	4 (67)	5 (83)	4 (67)	4 (67)

*Left cochleovestibular deficit, not related to study treatment.
**Subject discontinued treatment after the 2nd dose of ARB-1467 due to "HBV blip"(HBV-DNA 88 IU/mL) – ALT increase up to 627 U/L on Day 36 of the study associated with HEV super-infection. ALT returned to baseline by Day 60.

- Most AEs were mild and transient. Only two AEs were reported by two subjects; erythema (0.2 mg/kg) and upper respiratory tract infection (placebo). All other AEs were reported by single subjects
- Isolated elevated glucose, decreased lymphocytes and low phosphate values seen across all treatment groups, including placebo
- 17/18 (94%) subjects received all three monthly doses
- No infusion reaction AEs were reported

Individual ALT Values Over Time



- No significant changes in ALT were seen in any dose cohort
- One subject in Cohort 2 experienced a Grade 3 increase in ALT attributed to acute HEV super-infection

CONCLUSIONS

- Single-dose results demonstrate significant reductions in serum HBsAg levels at 0.2 mg/kg and 0.4 mg/kg
- Multi-dose results show a stepwise, additive reduction in serum HBsAg with each subsequent dose
  - Reductions of greater than 1 log_{10} IU/mL in 5/11 patients receiving 0.4 mg/kg dose
- No significant differences in serum HBsAg reductions between HBeAg-negative and HBeAg-positive patients
- Treatment has been generally well tolerated
- An additional cohort to evaluate the impact of alternative dosing frequency and duration on HBsAg reduction is ongoing (see clinicaltrials.gov)

ACKNOWLEDGMENTS

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