Bi-weekly Dosing of ARB-1467 LNP siRNA in HBeAg Negative, Virally Suppressed Patients with Chronic HBV Infection Leads to Deeper Declines in HBsAg and Potential Association with IL28b

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Arbutus BIOPHARMA Curing Chronic Hepatitis B

BACKGROUND

ARB-1467

- Novel RNA interference product
- Delivered via proprietary lipid nanoparticle (LNP) technology
- Generally safe and well tolerated

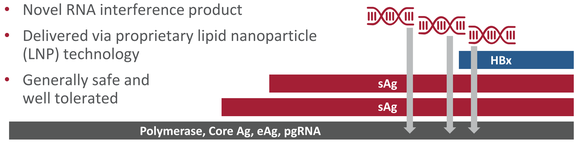


Figure 1: Unique 3-trigger design inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens

Introduction

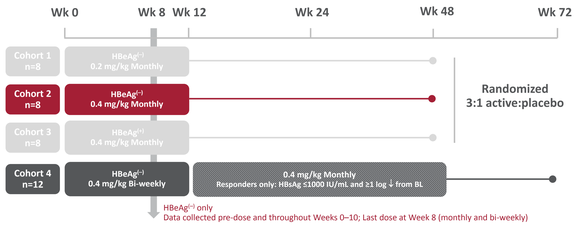
- Historically, quantitative HBsAg cutoff value of < 50 IU/mL and HBV DNA < 2000 IU/mL provided 100% sensitivity and 92% specificity in predicting the 2-year probability of HBsAg seroclearance[1]
- Significant reduction of HBsAg, irrespective of HBeAg status, was seen when ARB-1467 was given to nucleos(t)ide-treated patients in the ARB-1467-002 Phase 2 study (NCT02631096)[2]
  - Multi-dose results show a stepwise, additive reduction in serum HBsAg with each subsequent dose
  - Reductions of greater than 1 log10 IU/mL in 5/11 patients receiving 0.4 mg/kg dose
  - Generally safe and well tolerated

OBJECTIVES

- Primary: 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: To evaluate the antiviral activity of ARB-1467 for up to 72 weeks after the first dose of study treatment
- Analysis set: Preliminary results comparing monthly (Cohort 2) vs. bi-weekly (Cohort 4) dosing in HBeAg$^-$ subjects are being presented

STUDY DESIGN AND METHODS

Figure 2: ARB-1467-002 study design



Cohort 4 subjects continued to monthly dosing up to Treatment Week 48 if they met the following criteria (after 5 bi-weekly doses of ARB-1467):

- **Responder Criteria:** HBsAg ≤1000 IU/mL with ≥1 log10 decline during the first 10 weeks of treatment

- ARB-1467 or placebo given as a 2-hour IV infusion (Cohort 4 open-label)
- Broad inclusion criteria
  - Non-cirrhotic, chronic HBV infection receiving NA therapy with ETV or TDF for ≥ 12 months
  - HBsAg ≥ 1000 IU/mL, HBV-DNA negative
  - ALT or AST ≤ 2x ULN
  - Fibroscan ≤ 9 kPa
- Pre-medications given the evening prior and 30 minutes prior to each infusion
- Safety monitoring and HBV markers were performed throughout monthly and bi-weekly portions of the study

RESULTS

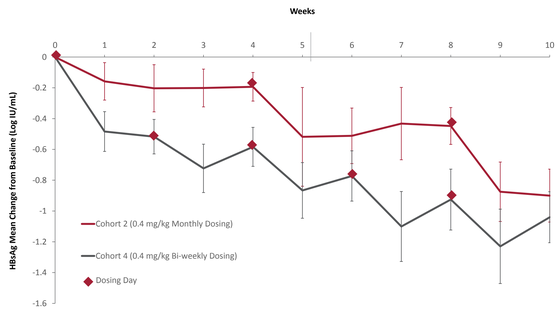
Demographics

Table 1: Baseline characteristics were similar across cohorts

	Cohort 1[a] HBeAg(–) 0.2 mg/kg Monthly n=6	Cohort 2 HBeAg(–) 0.4 mg/kg Monthly n=6	Cohort 3[a] HBeAg(+) 0.4 mg/kg Monthly n=6	Cohort 4 HBeAg(–) 0.4 mg/kg Bi-weekly n=12	Placebo n=6
Male, n (%)	4 (67)	4 (67)	6 (100)	9 (75)	5 (83)
Age, median (range) y	44 (28-52)	47 (31-64)	47 (32-52)	49 (29-64)	49 (40-54)
White, n (%)	4 (67)	4 (67)	3 (50)	4 (33)	3 (50)
Asian, n (%)	2 (33)	2 (33)	2 (33)	6 (50)	2 (33)
BMI, median (range) kg/m^2	24.6 (21-27)	26.8 (18-30)	28.7 (24-32)	24.2 (18-32)	25.2 (22-27)
ALT, median (range) IU/mL	28.5 (19-44)	31.5 (26-78)	38.5 (27-64)	29.5 (13-63)	29.5 (20-45)
HBsAg, mean (SD) log$_{10}$ IU/mL	3.5 (0.55)	3.4 (0.72)	3.0 (0.3)	3.6 (0.45)	3.3 (0.44)
HBV genotype[b]					
B	0	1 (17)	0	1 (8)	0
C	4 (67)	1 (17)	4 (67)	8 (67)	4 (67)
D	2 (33)	3 (50)	0	0	1 (17)
C/D	0	1 (17)	1 (17)	0	1 (17)
Undetermined[c]	0	0	1 (17)	3 (25)	0
IL28b genotype(rs12979860)[d]					
CC	0	0	0	8 (67)	0
CT	0	0	0	1 (8)	0
TT	0	0	0	2 (17)	0
Missing	6 (100)	6 (100)	6 (100)	1 (8)	6 (100)

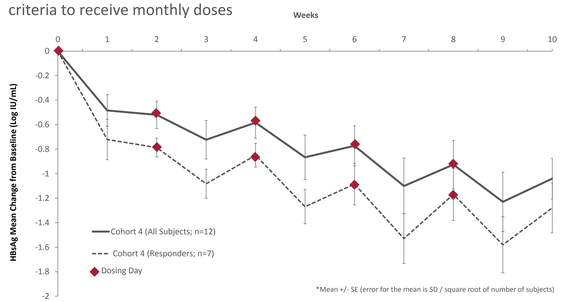
[a]Cohorts 1/3 [HBeAg(+)] are not included in these analyses.
[b]HBV genotype line probe assay (INNO-LiPA).
[c]Indeterminate result or unamplifiable sample.
[d]IL28b genotype not done in Cohorts 1-3.

Figure 3: Deeper HBsAg mean declines from baseline HBsAg level were observed in subjects with more frequent dosing (monthly vs bi-weekly)



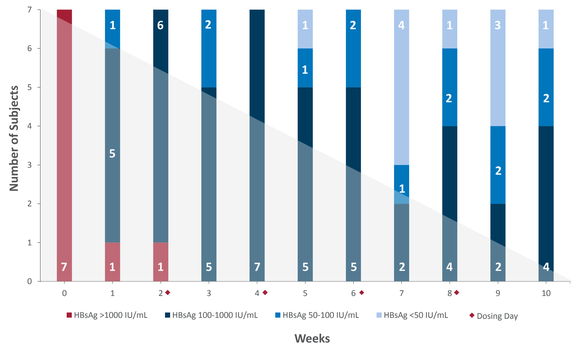
- All subjects experienced a significant reduction in HBsAg from baseline

Figure 4: HBsAg mean change* from baseline in subjects in Cohort 4 who met criteria to receive monthly doses



- 7 of 11 (64%) subjects were 'Responders' (met criteria to continue to monthly dosing)
- 5 of 7 (71%) subjects met Responder criteria after only 2 doses
- Maximum individual HBsAg decline was 2.7 log10 IU/mL

Figure 5: Number of subjects reaching HBsAg < 50 IU/mL by treatment week



- 5 of 7 (71%) Responders reached HBsAg < 50 IU/mL

Table 2: Factors associated with attaining response criteria

	Met Response Criteria (Responders) n=7	Did not meet Response Criteria n=5	P-value
Male, n (%)	6 (85.7)	3 (60)	0.5227
Median age, y (range)*	50 (47-60)	45 (35-51)	0.1155
White, n (%)	2 (28.6)	2 (40)	1.0000
Asian, n (%)	5 (71.4)	1 (20)	0.2424
Median BMI, kg/m^2 (range)	23.5 (19.3-31.7)	25.7 (18.4-31.5)	0.4894
Median ALT, IU/mL (range)	16 (13-63)	31 (29-55)	0.3089
Mean HBsAg log10 IU/mL (SD)	3.31(0.33)	3.90 (0.38)	0.0240
HBV genotype C, n (%)	4 (57.1)	4 (80)	1.000
IL28b genotype CC, n (%)	7 (100)	1 (20)	0.0242

- Baseline HBsAg and IL28b genotype CC were significantly ($p<0.025$) associated with Response

Safety

Table 3: Treatment-emergent adverse events

n (%)	Cohort 1 HBeAg(–) 0.2 mg/kg Monthly n=6	Cohort 2 HBeAg(–) 0.4 mg/kg Monthly n=6	Cohort 3 HBeAg(+) 0.4 mg/kg Monthly n=6	Cohort 4 HBeAg(–) 0.4 mg/kg Bi-weekly n=12	Placebo n=6
Any AE *Drug-related*	5 (83) *3 (50)*	5 (83) *4 (67)*	2 (33) *2 (33)*	8 (67) *4 (42)*	5 (83) *2 (33)*
Grade 3–4 AEs	1 (17)	0	0	0	0
Serious AEs	1 (17)[a]	0	0	0	0
Discontinuation for an AE	0	1 (17)[b]	0	1 (17)[c]	0
Grade 3–4 lab abnormalities[d]	4 (67)	5 (83)	4 (67)	9 (75)	4 (67)

[a] Left cochleovestibular deficit, not related to study treatment.
[b] Discontinued after the 2nd dose due to acute HEV super-infection and "HBV blip"(HBV-DNA 88 IU/mL)[3].
[c] Discontinued after the 3rd dose due to mild infusion reaction, arthralgia and hair loss.
[d] Isolated ↑ glucose, ↓ lymphocytes and ↓ phosphate in all groups including placebo.

- Most AEs to date have been mild and transient
- 17/18 (94%) subjects in Cohorts 1–3 received all three monthly doses
- 11/12 (92%) in Cohort 4 received all five bi-weekly doses

CONCLUSIONS

- All treated subjects experienced a reduction in HBsAg from baseline
- Greater HBsAg reductions were observed with more frequent dosing (maximum individual decline 2.7 log IU/mL)
- HBsAg values <50 IU/mL were achieved
- Baseline HBsAg and IL28b genotype CC were significantly associated with Response
- Initial results for the monthly dosing extension suggest that monthly dosing is not sufficient to maintain or improve initial reductions in s-antigen levels
- Treatment with ARB-1467 was generally well tolerated
- Combination therapy with other agents and longer treatment duration may be needed for a HBV functional cure

REFERENCES

1. Ungtrakul et al., Medicine (2017) 96:13.
2. Streinu-Cercel A, et al. *J Hepatol* 2017;66 (suppl 1):S688–S689.

CONTACT INFORMATION AND DISCLOSURES

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