RNA interference therapy with ARC-520 Injection results in long term off-therapy antigen reductions in treatment naïve, HBeAg positive and negative patients with chronic HBV

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INTRODUCTION

ARC-520 Injection, Arrowhead's first intravenous RNA interference drug, targets cccDNA-derived HBV mRNA expressed in the liver of chronic hepatitis B patients (CHB). Its design and preclinical characteristics (Wooddell et al., 2013) as well as its tolerability and pharmacokinetics in healthy volunteers (Schluep et al., 2017) have previously been described. More recently, single dose treatment of naïve HBeAg positive and HBeAg negative CHB and HBV infected chimpanzees demonstrated that HBsAg was expressed not only from the episomal cccDNA minichromosome but also from transcripts arising from HBV DNA integrated into the host genome, which was the dominant source in HBeAg-negative chimpanzees and CHB patients (Wooddell et al., 2017). Here we report additional antigen reductions observed off-therapy during a 12-month follow-up period in a subset of CHB that were enrolled in a multi-dose extension study.

AIM

Consensus is emerging in the field of HBV that functional cure (ie. sustained HBsAg loss after a finite therapy) is the preferred goal for new HBV therapies (Lok et al., 2017). This extension study was performed to evaluate if prolonged RNAi therapy in combination with entecavir (ETV) could lead to sustained antigen reductions, host control of the virus and HBsAg loss in CHB.

METHODS

Treatment naïve CHB enrolled in the Heparc-2001 study who previously received a single IV dose of 4 mg/kg ARC-520 and started daily ETV on the same day were eligible to participate in the extension study.

- 8 CHB (5 HBeAg-neg, 3 HBeAg-pos) received up to 9 doses of 4 mg/kg ARC-520 once every 4 weeks with daily ETV.
- Viral DNA, RNA and antigen knockdown (KD) were measured at regular intervals [qHBsAg, HB core-related antigen (qHBcrAg) in all, qHBeAg in HBeAg-pos].
- Patients continued their daily ETV post ARC-520 and were followed for an additional 12 months after the last ARC-520 dose.

REFERENCES

Lok, AS et al. Hepatitis B cure: From discovery to regulatory approval. *J Hepatol.* 2017 Oct;67(4):847-861.

Schluep, T et al. Safety, Tolerability, and Pharmacokinetics of ARC-520 Injection, an RNA Interference-Based Therapeutic for the Treatment of Chronic Hepatitis B Virus Infection, in Healthy Volunteers. *Clin Pharmacol Drug Dev*. 2017;6(4):350-62.

Wooddell, CI et al. Hepatocyte-targeted RNAi therapeutics for the treatment of chronic hepatitis B virus infection. *Mol Ther.* 2013 May;21(5):973-85.

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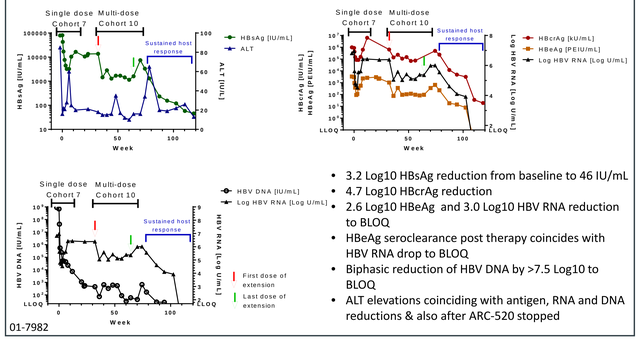
RESULTS

Case Study 1: HBeAg positive patient flared when ARC-520 stopped



- 3.2 Log10 HBsAg reduction from baseline to 46 IU/mL
- 4.7 Log10 HBcrAg reduction
- 2.6 Log10 HBeAg and 3.0 Log10 HBV RNA reduction to BLOQ
- HBeAg seroclearance post therapy coincides with HBV RNA drop to BLOQ
- Biphasic reduction of HBV DNA by >7.5 Log10 to BLOQ
- ALT elevations coinciding with antigen, RNA and DNA reductions & also after ARC-520 stopped

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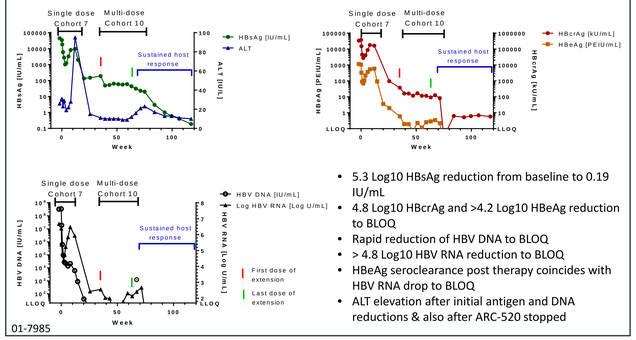
Case Study 2: HBeAg positive patient with HBsAg at 0.19 IU/mL



- 5.3 Log10 HBsAg reduction from baseline to 0.19 IU/mL
- 4.8 Log10 HBcrAg and >4.2 Log10 HBeAg reduction to BLOQ
- Rapid reduction of HBV DNA to BLOQ
- > 4.8 Log10 HBV RNA reduction to BLOQ
- HBeAg seroclearance post therapy coincides with HBV RNA drop to BLOQ
- ALT elevation after initial antigen and DNA reductions & also after ARC-520 stopped

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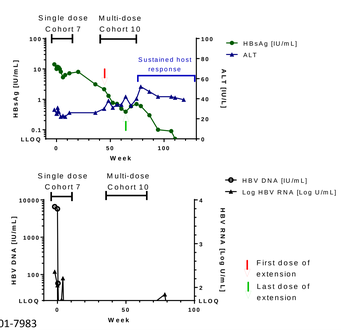
Case Study 3: HBeAg negative patient with HBsAg seroclearance



- >2.4 Log10 HBsAg reduction from baseline to BLOQ (HBsAg seroclearance)
- Delayed HBsAg response
- HBcrAg BLOQ throughout the study
- HBV RNA decreased rapidly from a low baseline to BLOQ after single dose of ARC-520 and then remained at or below LLOQ throughout the study
- Rapid reduction of HBV DNA to undetectable levels with ARC-520 plus entecavir
- Antigen decrease and seroclearance off ARC-520 coincided with a doubling of ALT, consistent with increased host response to virus

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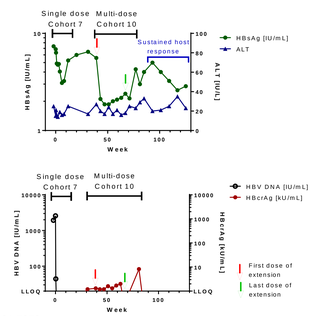
Case Study 4: HBeAg negative patient with host response post ARC-520



- 0.6 Log10 HBsAg reduction from baseline to NADIR, with rebound followed by additional reduction off-therapy
- Current HBsAg is 2.9 IU/ml
- HBV RNA BLOQ throughout study
- HBcrAg floating around LLOQ throughout study, except one spike post ARC-520
- Rapid reduction of HBV DNA to undetectable levels with ARC-520 plus entecavir

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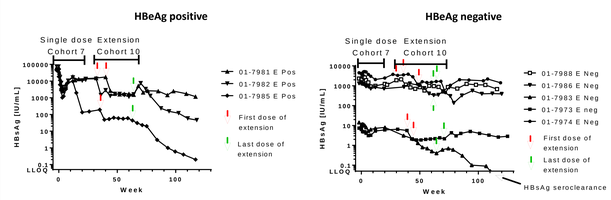
Log Antigen Reduction Summary through 12 Months of Follow-up

		NADIR Single Dose		NADIR Extension	
		HBeAg pos	HBeAg neg	HBeAg pos	HBeAg neg
Log HBsAg reduction from baseline	Average	-1.46	-0.33	-3.43	-1.10
	SEM	0.06	0.02	1.04	0.33
	Min	-1.40	-0.25	-1.74	-0.58
	Max	-1.58	-0.37	-5.31	-2.37
Log HBeAg reduction from baseline	Average	-1.37	NA	-2.86	NA
	SEM	0.10	NA	0.70	NA
	Min	-1.20	NA	-1.78	NA
	Max	-1.54	NA	-4.18	NA
Log HBcrAg reduction from baseline	Average	-1.17	-0.70	-4.19	-0.44
	SEM	0.10	NA	1.25	NA
	Min	-1.04	NA	-1.82	NA
	Max	-1.36	NA	-6.08	NA

HBsAg Summary



- 2/3 HBeAg pos showed strong virologic control off ARC-520
  - These strong responses corresponded to HBeAg seroclearance and loss of circulating HBV RNA
- 1/5 HBeAg neg showed HBsAg seroclearance event off ARC-520
- 1/5 HBeAg neg showed sustained host response off ARC-520
- This was despite the fact that ARC-520 was not ideal for HBeAg neg patients with high expression of HBsAg from integrated HBV DNA
- Productive host responses can be seen as early as following a single dose of RNAi trigger plus a NUC
- Productive host responses can correspond to subtle increases in ALT (eg 10 to 20 IU/L in case study 2)

Tolerability

- Mean number of ARC-520 doses in the extension was 7.6 with a range of 5 to 9
- 7/8 patients reported at least one mild AE
- No AEs were rated as serious, severe or caused withdrawal
- Most frequent AEs were mild fever and mild flu-like symptoms
- As of November 2016, ARC-520 and the NAG-MLP containing drug platform was discontinued due to animal toxicology findings, not due to safety signals in humans.

Adverse Event	N	Severity
Fever	5	mild
Flu-like symptoms	5	mild
Rash	2	mild
Influenza	1	mild
Haematuria	1	mild
Procedural pain	1	mild
Arthralgia	1	mild
Chest Discomfort	1	mild
Headache	1	mild
Running nose	1	mild
Epigastric discomfort	1	mild
Malaise	1	mild
Temporomandibular joint pain	1	mild

CONCLUSIONS

- ARC-520 was generally well tolerated
- ARC-520 + ETV were effective at rapidly suppressing HBV DNA
- A single dose of ARC-520 together with ETV reduced HBsAg for up to 44 weeks
- Multiple doses of ARC-520 resulted in additional HBsAg reductions in all patients, as much as 5.3 logs
- Consistent with our previous reports, ARC-520 was more active in HBeAg-positive patients, presumably due to more cccDNA-driven antigen production in treatment naïve HBeAg-positive and a higher fraction of qHBsAg from integrated DNA in HBeAg-negative patients
- Mild ALT elevations off ARC-520 therapy coincided with sustained host responses in 2/3 HBeAg-positive and 2/5 HBeAg negative patients
- One HBeAg-negative patient serocleared HBsAg post ARC-520
- Antigen reduction through RNAi in combination with oral ETV may lead to sustained control, HBsAg seroclearance and functional cure of chronic hepatitis B
- Sustained host responses were observed despite the fact that ARC-520 was not ideal, as it did not target HBsAg derived from integrated HBV DNA
- Clinical studies with the novel RNAi therapy ARO-HBV, designed to suppress viral RNA from all sources, are ongoing (see oral presentation by Dr. C. Wooddell, Abstract PS-030,12 April 2018 @ 17:15)