ARC-520 produces deep and durable knockdown of viral antigens and DNA in a phase II study in patients with chronic hepatitis B

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1. BACKGROUND

ARC-520 is a novel, short interfering RNA (siRNA)-containing, liver-targeted therapeutic for treatment of chronic hepatitis B virus (HBV) designed to reduce all cccDNA derived HBV transcripts via RNA interference. Viral proteins, in particular HBeAg and HBsAg, have been implicated in immune tolerance, sustained infection and disease progression. Therapies targeting viral proteins might allow host immune reconstitution, thereby promoting HBsAg seroclearance. A Phase I study in healthy subjects has demonstrated the safety profile of ARC-520.

2. MATERIALS & METHODS

Table 1: Study cohorts and status

Cohort	Prior ETV	Pat Type	ARC-520 dose	Active / PBO	Baseline HBsAg mean (range)‡	Status
1	Yes**	HBeAg neg	1.0 mg/kg	6/2	3.4 (3.0-4.2)	Complete/Unblinded
2	Yes**	HBeAg neg	2.0 mg/kg	6/2	3.5 (3.2-4.3)	Complete/Unblinded
3	Yes**	HBeAg neg	3.0 mg/kg	6/2	3.6 (3.1-4.0)	Complete/Unblinded
4	Yes**	HBeAg neg	4.0 mg/kg	6/2	3.4 (3.2-4.0)	Complete/Unblinded
5	Yes**	HBeAg pos	4.0 mg/kg	6/2	3.6 (3.1-4.2)	Complete/Unblinded
6*	Yes**	HBeAg pos	2 x 2.0 mg/kg	6/0	3.3 (3.0-3.6)	Complete/Open label
7	No	HBeAg pos HBeAg neg	4.0 mg/kg	6/0 6/0	4.4 (3.1-4.9) 2.9 (0.8-3.6)	Ongoing / Open label

* two doses two weeks apart; ** > 6 months; ‡ Log IU/mL for active subjects; PBO = normal saline

- Adult patients with HBeAg negative or positive chronic HBV, ALT/AST < 100 IU/mL and Fibroscan ≤ 8 at screening.
- Treatment naïve patients started daily oral entecavir concomitantly with intravenous ARC-520 and continued throughout the study.
- Entecavir (ETV) experienced patients had HBsAg >1000 IU/mL (cohorts 1-4) or >500 IU/mL (cohorts 5-6) and HBV DNA < LLOQ at baseline.

3. OBJECTIVES

Primary Objective:

- Depth and duration of HBsAg reduction in response to a single dose or two doses (cohort 6) of ARC-520 in combination with entecavir

Additional Objectives:

- Safety and tolerability of escalating single doses of ARC-520 co-administered with a fixed dose of entecavir
- Multiple additional secondary and exploratory endpoints

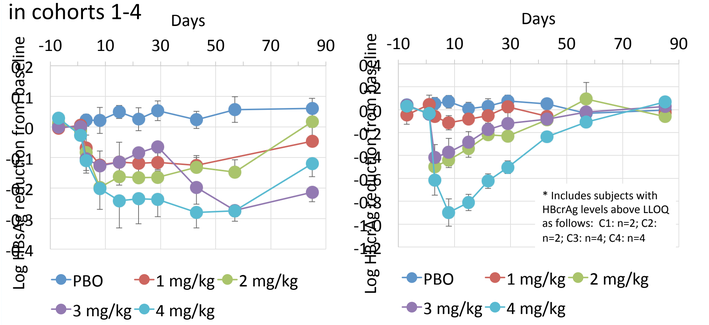
5. RESULTS

- Fifty-eight patients have been successfully dosed with 48 receiving drug and 10 receiving placebo. 20 females and 38 males were enrolled, all of Chinese ethnicity, with a mean age of 41 years (range of 23 to 59).
- To date there have been no serious AEs, no dose limiting toxicities, no discontinuations due to medication AEs, and a modest occurrence rate (23%) of AEs. All reported AEs were deemed unrelated to study drug by the PI.
- Low occurrence rate of abnormal laboratory tests, with no observed relationship to timing or dose.
- Treatment naïve patients reduced viral DNA up to 4.3 log (mean 2.2 log) after ARC-520 and ETV.

Table 2. Treatment emergent adverse events

Adverse Event	1 mg/kg n=6	2 mg/kg n=6	3 mg/kg n=6	4 mg/kg n=24	2 mg/kg x2; n=6	PBO n=10
All	1	5	1	2	1	0
Extravasation		1 mild				
Malaise		1 mod				
Influenza	1 mild					
Blood CK increase		1 mild				
Diabetes Mellitus		1 mild				
Pain in extremity			1 mild			
Presyncope		1 mod				
Headache				1 mild		
Dizziness				1 mild		
Fever					1 mild	

Figure 1. Log reduction in HBsAg and HBV core related antigen (HBcrAg) in cohorts 1-4



5. RESULTS (cont.)

Figure 2. Reduction in HBsAg, HBeAg and HBcrAg in cohort 5

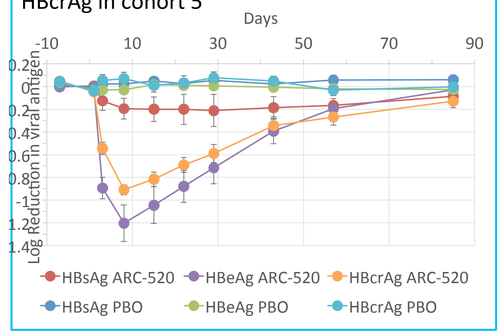
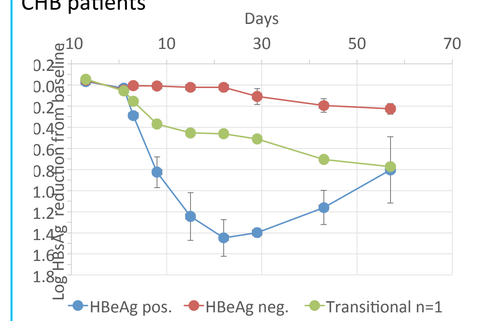


Table 3. Max reduction in viral antigens

				Log reduction from baseline Mean (max)		
Cohort	Dose [mg/kg]	HBeAg status	Prior ETV	HBsAg	HBcrAg	HBeAg
1	1	Neg	Y	-0.2 (-0.3)*	-0.2 (-0.2)	N/A
2	2	Neg	Y	-0.2 (-0.3)*	-0.5 (-0.5)	N/A
3	3	Neg	Y	-0.3 (-0.4)*	-0.4 (-0.7)	N/A
4	4	Neg	Y	-0.4 (-0.5)*	-0.9 (-1.1)	N/A
5	4	Pos	Y	-0.3 (-0.7)*	-0.9 (-1.1)	-1.2 (-1.7)
6‡	2x2	Pos	Y	-0.5 (-0.8)+	-0.7 (-1.2)	Pending
7‡,†	4	Pos	N	-1.5 (-1.9)+	Pending	Pending
7‡	4	Neg	N	-0.2 (-0.4)+	Pending	N/A

*Roche Elecsys batch analyzed data set + Abbott Architect data ‡ Preliminary data, analysis is ongoing † Excluding transitional patient

Figure 3. Reduction in HBsAg in treatment naïve CHB patients



- HBeAg-neg., ETV experienced patients showed a dose response in HBcrAg; qHBsAg dose response was less pronounced.
- HBeAg-pos, ETV experienced patients had a substantially higher reduction in HBeAg and HBcrAg compared to HBsAg.
- Divided doses at 4 mg/kg were similar to a single dose (data not shown).
- Best qHBsAg reduction was seen in naïve HBeAg-pos patients; HBeAg-neg showed a delayed response.
- Transitional patient was HBeAg-pos. at baseline and HBeAg negative at days 3 to 43.

- Variations in viral antigen reduction are consistent with lower levels of cccDNA derived mRNA transcripts in chronic ETV patients and HBeAg-neg.

6. SUMMARY

- ARC-520 effectively reduced viral antigens derived from cccDNA by up to 1.9 logs (99%).
- ARC-520 was well tolerated.
- Direct antiviral effect lasted up to 57 days after a single dose, delayed response duration >57 days.
- Findings consistent with higher cccDNA-driven antigen production in naïve HBeAg-pos CHB.
- Chronic ARC-520 studies aimed at producing HBsAg seroclearance are underway.

7. DISCLOSURES

- **Man-Fung Yuen** – BMS, Gilead, GSK, Roche diagnostics (Advisory Board (AB) & Speaker); ARC (Grant)
- **Henry LY Chan** – Abbvie, BMS, Gilead, Novartis, Roche (AB & Speaker), Jansen (AB); Echosens (Speaker), Roche (unrest. grant)
- **Kevin Liu** – None
- **Bruce D. Given, James Hamilton, Thomas Schluep** - Arrowhead Research Corp. (ARC) (Employment)
- **Ching-Lung Lai** – ARC, Gilead, Abbvie (AB); Gilead, Abbvie, BMS (Sponsored Lectures)
- **Stephen A. Locarnini** – ARC, Gilead (AB, Contract Research)
- **Johnson YN Lau** - ARC (AB)
- **Carlo Ferrari** – ARC (AB), Gilead, Roche, Transgene, Abivax, Medimmune (AB, consultant), Gilead (Grant)
- **Robert G. Gish** - ARC (Options, AB),