A phase 1 study to evaluate safety and tolerability of escalating single doses of the HBV RNA interference drug ARC-521 in a healthy volunteer and HBV patient population

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INTRODUCTION

Safety and antiviral activity of single, ascending doses of ARC-520, a RNA interference therapeutic for chronic Hepatitis B virus (HBV) that targets only cccDNA-derived mRNA have been reported previously[1]. ARC-521 targets both mRNA transcribed from HBV cccDNA and integrated DNA-derived mRNA transcripts through an RNAi mechanism. We report the safety and tolerability of ARC-521 administered as single escalating i.v. doses to healthy volunteers as well as safety and activity of single and multiple doses of ARC-521 in HBV patients.

PRIMARY OBJECTIVES

- Determine incidence and frequency of adverse events possibly or probably related to treatment as a measure of the safety and tolerability of ARC-521 at escalating single and multiple doses.
- Evaluate single-dose pharmacokinetics of ARC-521 in healthy volunteers.
- Measure reduction of viral antigens and DNA in response to ARC-521.

METHODS

- Cohorts 1-6: male and female adult healthy volunteers (HVs) age 18-55, BMI 19-35 kg/m^2 with 6 subjects enrolled per cohort (4 active, 2 placebo).
- Healthy volunteers received single escalating doses of 0.6, 1.0, 2.0, 4.0, 5.0, and 6.0 mg/kg of ARC-521. Safety parameters were followed through Day 29.
- All dose escalations were approved by a Drug Safety Committee.
- Cohorts 3b/c, 4b/c and 6b/c enrolled 4 NUC naïve (b) or 4 NUC experienced (c) HBeAg negative CHB patients in an open label fashion.
- CHB patients were enrolled to receive up to three doses (Q28 days) of ARC-521 at escalating dose levels of 2.0, 4.0 and 6.0 mg/kg.
- HBsAg, HBcrAg and HBV DNA were analysed at various time points.
- All participants were pretreated with oral antihistamine and acetaminophen 2 hours prior to ARC-521 dosing.
- Study was stopped prematurely due to animal toxicology findings, not due to clinical safety issues.

RESULTS

Healthy Volunteer Results:

24 HVs received single doses of ARC-521, 12 received placebo

- 62.5% of active and 83% of placebo subjects reported at least one AE.
- No deaths, no dropouts due to AEs and no serious or severe AEs were reported in HVs.
- No infusion reactions or laboratory abnormalities were reported as AEs. No clinically significant ALT elevations were reported.

Table 1: HV treatment emergent AEs (>5%) by dose

AE	0.6 mg/kg n=4	1.0 mg/kg n=4	2.0 mg/kg n=4	4.0 mg/kg n=4	5.0 mg/kg n=4	6.0 mg/kg n=4	#(%) Active n=24	#(%) PBO n=12
Myalgia				1 mild	1 mild		2(8.3)	1(8.3)
Abdominal Pain/Discomfort			1 mild		1 mild		2(8.3)	1(8.3)
Presyncope		1 mild	1 mild		1 mild		3 (12.5)	0
Headache		1 mild		1 mild	1 mild		3 (12.5)	2 (16.7)
Lethargy				1 mild	2 mild		3 (12.5)	1(8.3)
Oropharyngeal Pain		1 mild		1 mild			2(8.3)	0
Nausea				1 mild	1 mild		2(8.3)	0

CHB Patient Results:

11 CHB patients received either one (4), two (2) or three (5) doses of ARC-521

- 4 enrolled to 3b and 3c each, 2 enrolled to 4b, 1 enrolled to 4c.
- 27.3% of CHB patients reported at least one AE possibly related to drug.
- No deaths or dropouts due to AEs were reported. One severe migraine exacerbation and one severe transaminase elevation (SAE) were reported.
- This SAE (possibly related) of elevated transaminases (ALT 678 U/L) was reported in a patient one month after receiving one 4 mg/kg dose of ARC-521 in the setting of NUC non-adherence and HBV DNA of 7.5 log10 IU/L.

Table 2: HBV patient treatment emergent AEs by dose

AE	2.0 mg/kg, n=8 (3b/3c)	4.0 mg/kg, n = 3 (4b/4c)	#(%) Active n=11
Increased Transaminases		1 severe	1(9)
Seasonal Allergy	1 mild		1(9)
Hematoma	1 mild		1(9)
Contusion		1 mild	1(9)
Back Pain	1 mild		1(9)
Syncope		1 mild	1(9)
Eczema	1 mild		1(9)
Dizziness	1 mild	1 mild	2(18)
Nausea	1 mild	1 mild	2(18)
Epistaxis	1 mild		1(9)
Renal colic	1 mild		1(9)
Flu	1 mild		1(9)
Thermal burn		1 mild	1(9)
Catheter site bruise	1 mild		1(9)
Migraine Exacerbation	1 severe		1(9)
Fatigue	1 mild		1(9)
Dysguesia	1 mild		1(9)

Figure 1a: Individual patient HBsAg reduction in patients receiving ARC-521 + chronic NUC (approx. 1-4 years of prior NUC use)

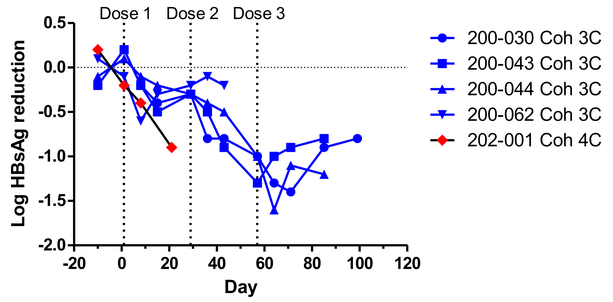


Figure 1b: Mean HBsAg reduction in patients receiving ARC-521 + chronic NUC (approx. 1-4 years of prior NUC use)

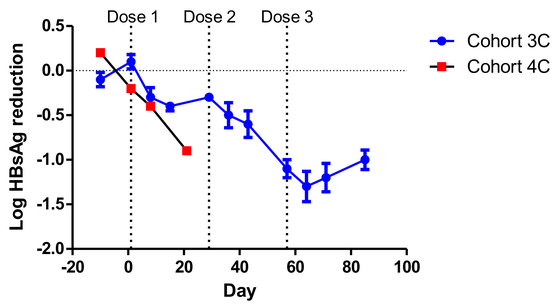


Figure 2: HBV DNA reduction in patients receiving ARC-521 alone

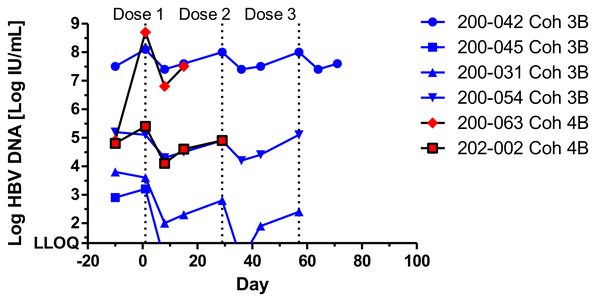


Figure 3: HBsAg reduction in patients receiving ARC-521 alone

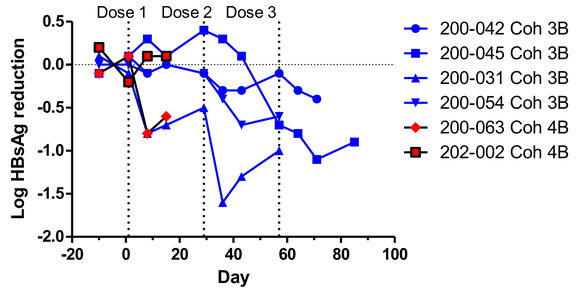
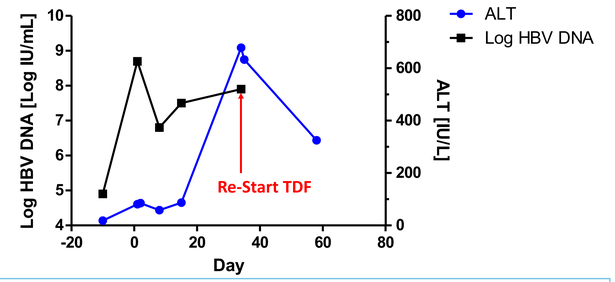


Figure 4: Patient with transaminase increase (cohort 4B) had a significant HBV DNA increase prior to and fluctuations during ARC-521 therapy



CONCLUSIONS

- ARC-521 was generally well tolerated in healthy volunteers and CHB patients.
- One SAE of elevated transaminases occurred in a CHB patient 1 month after single ARC-521 dose which may have been due to viral flare secondary to fluctuating HBV DNA and NUC non-adherence.
- Potent reductions in HBsAg and HBV DNA were seen in response to ARC-521.
- RNAi therapy benefits from combination with NUCs.
- Program discontinued due to EX-1 associated findings in non-clinical studies which were not seen in clinical trials. Development of ARO-HBV which contains no EX-1 is underway.

REFERENCES

1. Yuen MF et al. Differential reductions in viral antigens expressed from cccDNA vs integrated DNA in treatment naïve HBeAg positive and negative patients with chronic HBV after RNA interference therapy with ARC-520, EASL 2016.