First results with RNA interference (RNAi) in chronic hepatitis B (CHB) using ARO-HBV

Edward Gane[1], Stephen A. Locarnini[2], Tien Huey Lim[3], Simone Strasser[4], William Sievert[5], Wendy Cheng[6,7], Alexander Thompson[8], Bruce Given[9], Thomas Schluep[9], James Hamilton[9], Zhen Li[9], Gavin Cloherty[10], Danny Wong[11], Christian Schwabe[1], Kathy Jackson[2], Carlo Ferrari[12], Ching-Lung Lai[11], Robert G. Gish[13,14], Man-Fung Yuen[11]

1. Auckland Clinical Studies, Auckland, New Zealand 2. Victorian Infectious Disease Reference Laboratory, Victoria, Australia 3. Middlemore Hospital, Auckland, New Zealand 4. Royal Prince Alfred Hospital, Sydney, Australia 5. Monash Health and Monash University, Melbourne, Australia 6. Royal Perth Hospital, Perth, Australia 7. Linear Clinical Research, Perth, Australia 8. St. Vincent's Hospital, Melbourne, Australia 9. Arrowhead Pharmaceuticals, Pasadena, CA. USA 10. Abbott Diagnostics, Abbott Park, IL, USA 11. The University of Hong Kong, Hong Kong, China 12. University of Parma, Parma, Italy 13. Stanford University, Palo Alto, CA, USA 14. The Hepatitis B Foundation, Doylestown, PA, USA

INTRODUCTION

RNAi has shown promise as a potential component of finite therapy for patients with chronic hepatitis B (CHB) based on its ability to silence HBV mRNA thereby reducing all viral products, most notably HBsAg. Clinical utility has been limited by IV delivery and/or safety concerns. ARO-HBV is composed of two siRNAs, each directly conjugated to N-acetyl galactosamine to drive hepatocyte delivery. Administered subcutaneously (SQ), it is designed to silence all mRNA from cccDNA and host integrated viral DNA, without need for additional delivery elements.

AIM

AROHBV1001 is a double blind, single dose escalating study in healthy volunteers (NHV) and open label, multi-dose escalating study in patients with chronic HBV infection (CHB, NCT03365947). Objectives for this study are:

- Safety and tolerability of ARO-HBV in NHV and CHB.
- Single dose pharmacokinetics of ARO-HBV in NHV.
- Reduction of HBsAg from day 1 to post-dose nadir in CHB.
- Multiple additional exploratory objectives.

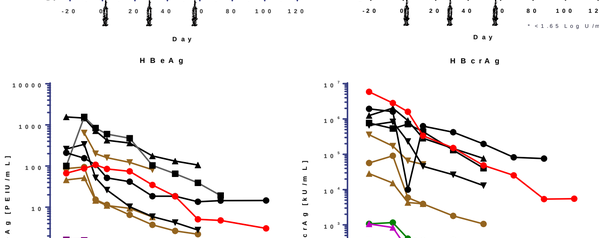
METHODS

This interim analysis reports on all single dose NHV cohorts and initial CHB cohorts that received monthly doses of ARO-HBV and had > 6 weeks of HBsAg assay results.

- NHV cohorts (4 active, 2 placebo) received single SQ doses of 35, 100, 200, 300, or 400 mg ARO-HBV or normal saline in a blinded fashion (cohorts 1-5).
- CHB cohorts 2b-5b (4 active) were HBeAg positive or negative, NUC naïve or NUC experienced at baseline, and received three monthly SQ doses of 100, 200, 300, or 400 mg ARO-HBV.
- CHB cohorts 8 and 9 (4 active) were HBeAg positive, treatment naïve or NUC experienced, respectively, that received three monthly SQ doses of 300 mg ARO-HBV.
- NUC experienced CHB patients continued their daily NUC throughout the study and NUC naïve CHB patients started daily NUC on day 1.
- For CHB, viral DNA (Roche Cobas, LLOQ 20 IU/mL), viral RNA (Abbott m2000, LLOQ 1.65 Log U/mL, Butler 2018) and antigens (qHBsAg (Roche Elecsys, LLOQ 0.05 IU/mL), qHBeAg (Diasorin Liaison, LLOQ 0.01 PEIU/mL), qHBcrAg (Fujirebo Lumipulse, LLOQ 1 kU/mL)) were measured periodically.
- Virologic results reported are through 56 days after 3rd dose (day 113) when available or most recent.
- Here we report on safety and tolerability in all NHV and safety, tolerability and virologic assessments in CHB cohorts 2b-5b, 8 and 9. Single dose PK in NHV will be reported elsewhere.

RESULTS

Mean Log HBsAg change from day 1 (n=4 per cohort)



*Previously reported 4 Log reduction in one 100 mg patient reduced to 2 Log upon re-assay

- Baseline HBeAg for cohorts 2b-5b: 2b (3E-/1E+), 3b (4E-), 4b (3E-/1E+), 5b (3E-/1E+)

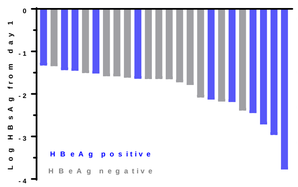
NADIR HBsAg responses for patients with > 6 weeks of HBsAg data

- > 1 log (90%) reduction 100%
- > 1.5 log (97%) reduction 83%
- > 2 log (99%) reduction 38%
- > 3 log (99.9%) reduction 3%

Individual changes in HBV DNA, HBV RNA, HBeAg and HBcrAg

- Colors in graphs below indicate cohorts as follows: Red (C2b), orange (C3b), purple (C4b), green (C5b), black (C8), brown (C9), HBeAg positive (solid line), HBeAg negative (dashed line)

NADIR Log HBsAg reduction by patient



- All patients received 3 monthly doses of ARO-HBV and had > 6 weeks of HBsAg data
- Range of NADIR: -1.3 to -3.8 Log_{10}
- Mean NADIR: -1.9 Log_{10}
- Similar responses observed for HBeAg positive and negative patients
  - Mean HBeAg positive (n=11): - 2.1 Log_{10}
  - Mean HBeAg negative (n=13): -1.8 Log_{10}

Safety and Tolerability

AEs in Healthy Volunteers	Cohort 1 35 mg	Cohort 2 100 mg	Cohort 3 200 mg	Cohort 4 300 mg	Cohort 5 400 mg	All Active	All PBO	Total AEs
AE Reported Terms	AROHBV n = 4	AROHBV n = 4	AROHBV n = 4	AROHBV n = 4	AROHBV n = 4	AROHBV n= 20	Placebo n= 10	
Hot flush, Feeling hot, Subjective Pyrexia	1			1		2	1	3
Headache	1	2	1	1	2	7	2	9
Abdominal pain	1	2	1			4	1	5
Upper respiratory tract infection	1	1			2	4	2	6
Lethargy, Fatigue		1	2			3	2	5
Myalgia		1				1	1	2
Sore Throat		1	1			2	2	4
Sensation of feeling dehydrated		1				1	1	2
Discomfort / bruising at cannula site		1		2	1	4	1	5
Nausea		1	1	2		4	1	5
Dizziness, Lightheadedness, Vertigo		1				1	2	3
Flu like illness, Non Specific Viral Illness		1	1			2		2
Emesis			1	1		2	1	3
Bruising / tenderness at injection site				1	1	2		2
Total AEs in >1 NHV	4	13	8	8	6	39	17	56

AEs in HBV Patients	Cohort 2b 100 mg	Cohort 3b 200 mg	Cohort 4b 300 mg	Cohort 5b 400 mg	Cohort 8 300 mg	Cohort 9 300 mg	Total AEs n=24
AE Reported Terms	AROHBV n = 4	AROHBV n = 4	AROHBV n = 4	AROHBV n = 4	AROHBV n = 4	AROHBV n= 4	
Insect bites	1		1				2
Upper respiratory infection, sore throat	1		1		1		3
Erythema, redness, hematoma, rash at injection site			1	2	2	2	7
Acne					2		2
Headache			2				2
Raised creatine kinase			1		1		2
Diarrhea			1	1			2
Lower back ache/pain			1		1		2
Total AEs in >1 CHB	2	0	8	3	7	2	22

NHV (single dose)

- 70% active v 80% PBO reporting at least one AE
- No AEs were rated as serious, severe or caused withdrawal
- No pattern of adverse changes in laboratory values
- Most frequent AE was headache (35% of active). No dose-dependent increase in frequency or severity of AEs.
- Two NHV reported mild AEs at injection site: One mild bruise at injection site, one mild tenderness at injection site

CHB (Multiple doses)

- 24 patients in cohort 2b-5b, 8 and 9 have received 3 monthly doses (400mg highest dose administered)
- No SAEs reported, no dropouts
- No dose related pattern of adverse changes in laboratory values (e.g. ALT, AST, total bilirubin, creatinine)
- AEs at injection site (rash, erythema, bruising/hematoma, tenderness) reported with approximately 12% of injections, all of which were mild

CONCLUSIONS

- ARO-HBV administered subcutaneously appears to be well tolerated at single or multiple monthly doses up to 400 mg.
  - Mild injection site reactions were observed with approximately 12% of subcutaneous injections.
- Strong HBsAg responses were observed in all HBV patients with monthly SQ doses and were similar in HBeAg positive and HBeAg negative patients and in NUC naïve and NUC experienced patients.
  - Range of HBsAg reductions from -1.3 to -3.8 Log_{10}.
  - Responses increasing with each dose in most patients.
  - This is an improvement over results with the first generation compound ARC-520, which only targeted HBV transcripts derived from cccDNA and showed better activity in HBeAg positive, NUC naïve CHB compared to other populations (Wooddell, 2017).
  - HBsAg responses observed with ARO-HBV are consistent with its ability to silence HBV mRNA from cccDNA and host integrated viral DNA. Host integrated viral DNA is a major source of HBsAg in certain CHB populations (Wooddell, 2018).
- No strong dose response was observed at doses between 100 mg and 400 mg ARO-HBV; additional patients are being added to cohorts to better elucidate dose response.
- Virologic responses are generally slower than observed with previous generation compounds using endosomal escape (Yuen, 2018).
- As expected, all other virologic parameters (HBV DNA, HBV RNA, HBeAg, HBcrAg) showing responses to ARO-HBV.
- ARO-HBV has characteristics desirable for RNAi to become a cornerstone therapy in finite regimens aimed at HBsAg clearance in patients with chronic HBV.

REFERENCES

Butler, EK et al. Utility of a new HBV RNA assay in HBeAg positive and negative CHB and following HBsAg seroclearance in patients treated with ARC-520, an RNAi drug targeting cccDNA derived HBV mRNA, *J Viral Hepat.* 2018;25(Suppl. 2):190-210

Wooddell, CI et al. RNAi-based treatment of chronically infected patients and chimpanzees reveals that integrated hepatitis B virus DNA is a source of HbsAg. *Sci Transl Med.* 2017 Sep;27(9):409.

Yuen, MF et al. 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. *J Hepatol.* 2018;68(S1):S526.