RNA Interference (RNAi) in Chronic Hepatitis B (CHB): Data from Phase 2 Study with JNJ-3989

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INTRODUCTION

RNAi with JNJ-3989 (formerly ARO-HBV) shows promise in CHB by silencing HBV RNA from cccDNA and integrated HBV DNA, reducing all viral products, including HBsAg.

OBJECTIVES

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 are:

- Safety and tolerability of JNJ-3989 in NHV and CHB.
- Single dose pharmacokinetics of JNJ-3989 in NHV.
- Reduction of HBsAg from day 1 to post-dose nadir in CHB.
- Multiple additional exploratory objectives.

METHODOLOGY

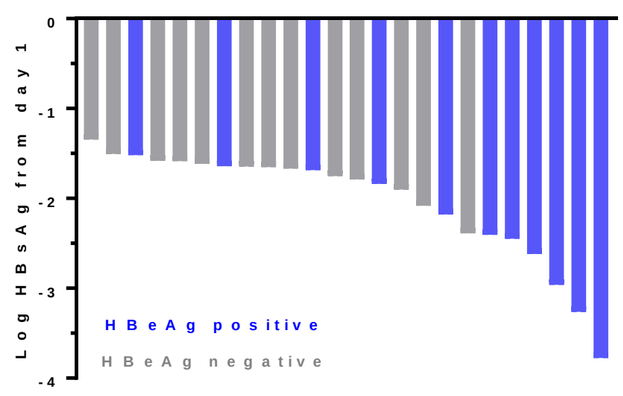
This interim analysis reports antiviral activity and safety in initial CHB cohorts that had 16 weeks of HBsAg assay results.

- CHB cohorts 2b-5b 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 JNJ-3989.
- CHB cohorts 8 and 9 were HBeAg positive, treatment naïve or NUC experienced, respectively, that received three monthly SQ doses of 300 mg JNJ-3989.
- NUC experienced CHB patients continued their daily NUC throughout the study and NUC naïve CHB patients started daily NUC on day 1.
- Viral DNA (LLOQ 20 IU/mL), viral RNA (LLOQ 1.65 Log U/mL) and antigens (qHBsAg (LLOQ 0.05 IU/mL), qHBeAg (LLOQ 0.01 PEIU/mL), qHBcrAg (LLOQ 1 kU/mL)) were measured periodically.

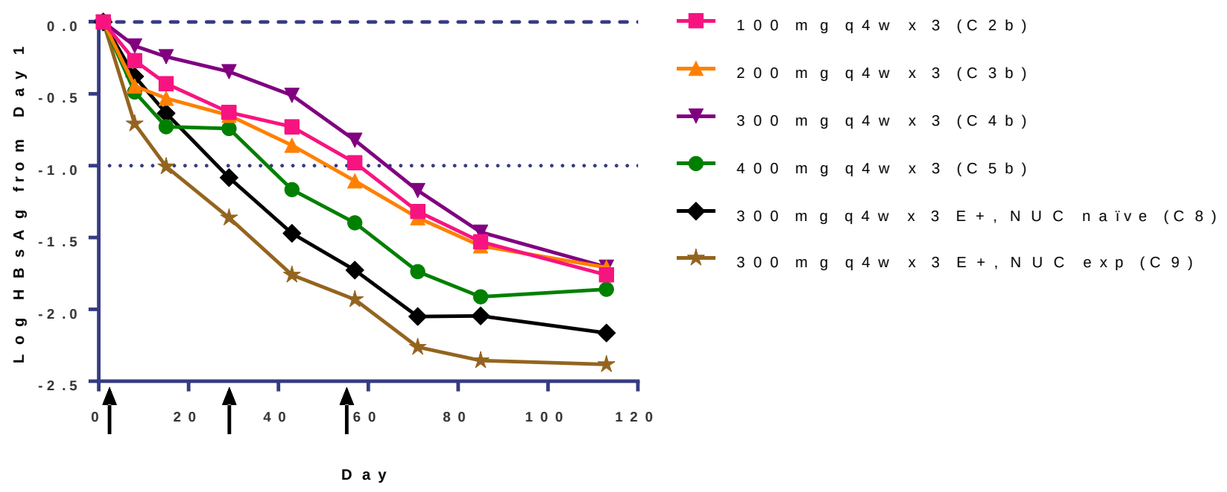
RESULTS

Baseline Demographics in CHB 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
Number CHB in cohort	4	4	4	4	4	4	24
HBeAg pos / HBeAg neg	1 / 3	0/4	1 / 3	1 / 3	4 / 0	4 / 0	11 / 13
NUC experienced	2	4	4	4	0	4	18
Race (Asian/Pacific Islander/Other)	4 / 0 / 0	4 / 0 / 0	4 / 0 / 0	4 / 0 / 0	3 / 1 / 0	4 / 0 / 0	23 / 1 / 0
Genotype (B / C / Unknown)	2/ 0 / 2	0 / 0 / 4	0 / 0 / 4	0 / 0 / 4	2 / 2 / 0	0 / 0 / 4	4 / 2 / 16
Mean baseline HBsAg (SEM) [IU/mL]	2,808 (2,540)	659 (310)	732 (295)	1,128 (625)	137,795 (88,141)	7,358 (2,726)	26,159 (16,731)

NADIR Log HBsAg reduction by patient



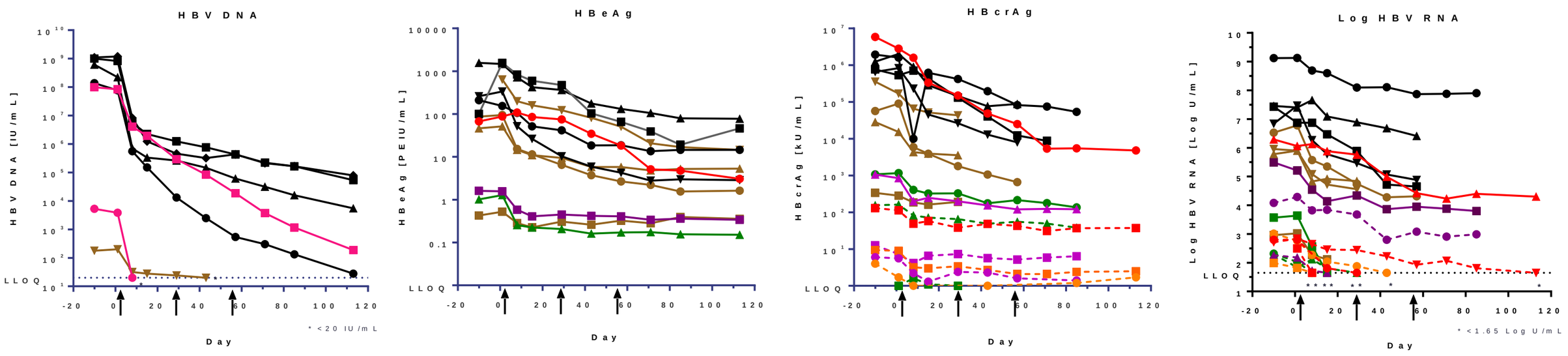
Mean Log HBsAg change from day 1



- All patients received 3 monthly doses of JNJ-3989 and had 16 weeks of HBsAg data
- Range of HBsAg NADIR: -1.3 to -3.8 Log_{10}
- Mean HBsAg NADIR: -2.0 Log_{10}
- All CHB patient's HBsAg responded
  - Mean HBeAg positive (n=11): -2.5 Log_{10}
  - Mean HBeAg negative (n=13): -1.8 Log_{10}

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

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



Safety and Tolerability

AE reported terms	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
Insect bites	1		1				2
Upper respiratory infection, sore throat	1		1		1	1	4
Erythema, redness, hematoma, rash at injection site			2	2	2	1	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	9	3	7	2	23

- 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

- JNJ-3989 administered subcutaneously appears to be well tolerated at monthly doses up to 400 mg.
- Monthly RNAi effectively reduced all measurable viral products. Strong HBsAg responses were observed in all HBV patients.
  - HBeAg positive CHB patients showed a moderately larger HBsAg reduction than HBeAg negative patients.
- No dose response was observed between 100 mg and 400 mg; additional patients are being added to cohorts to better elucidate dose response.
- JNJ-3989 has characteristics desirable for RNAi to become a cornerstone therapy in finite regimens aimed at HBsAg clearance in patients with chronic HBV.