Short term RNA interference (RNAi) therapy in chronic hepatitis B (CHB) using JNJ-3989 brings majority of patients to HBsAg <100 IU/ml threshold

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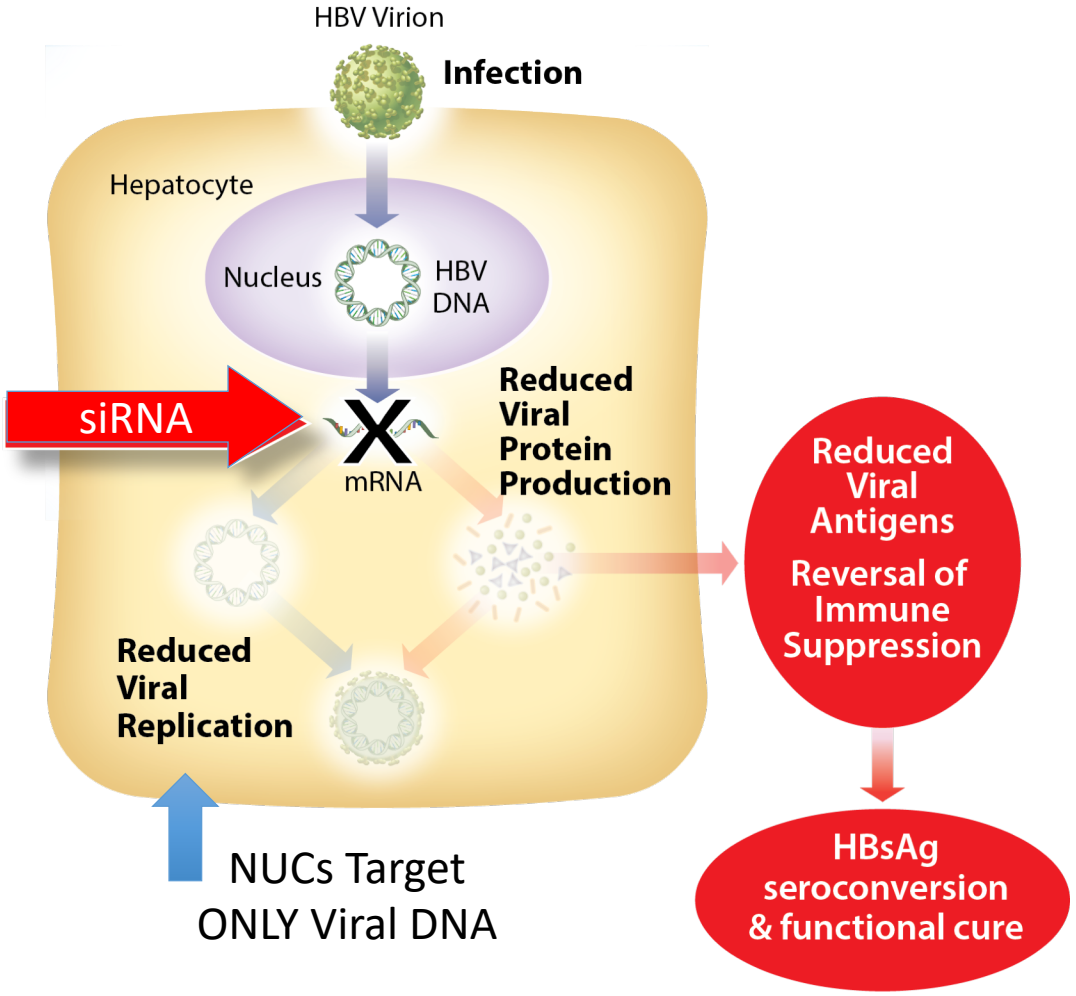
Simplified theory of an HBV RNAi therapeutic



Silence Entire HBV Genome

1. "HBsAg Theory"
   - Reducing HBsAg enables host immune system de-repression and long term control of virus
2. Destabilizing Viral Function
   - Silencing all antigens and reducing pgRNA could destabilize normal viral function
   - Enable host immune system de-repression and long term control of virus

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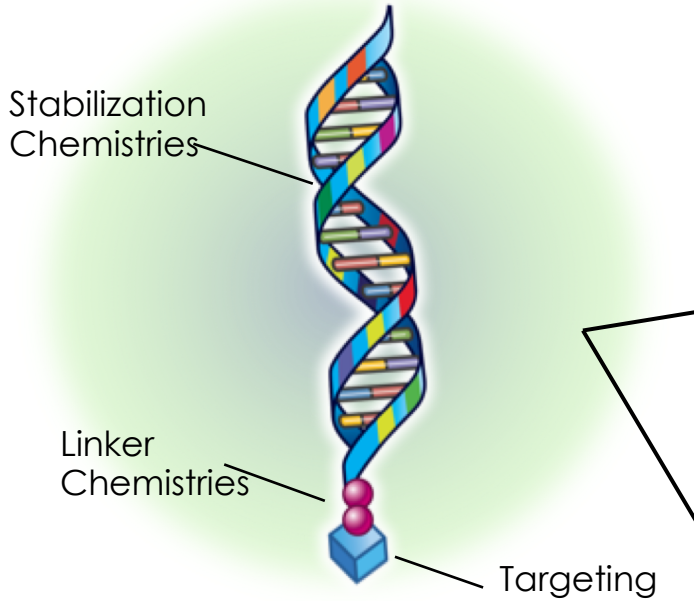
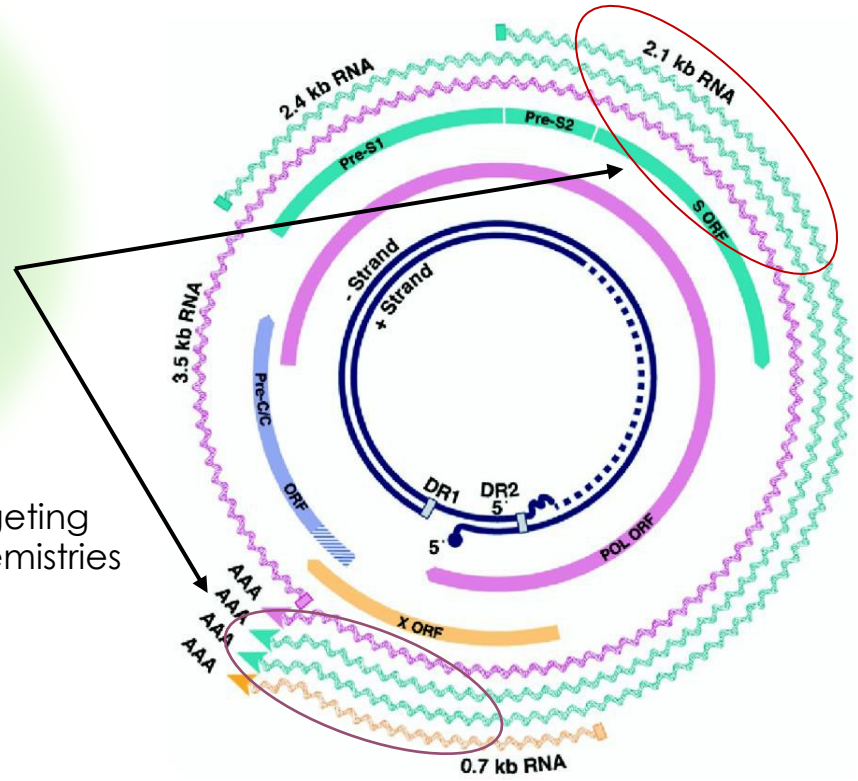
JNJ-3989 (ARO-HBV): Key design elements

- **Addresses full HBV transcriptome**
  - **Two hepatocyte targeted RNAi molecules**
  - **Works for cccDNA and integrated-derived transcripts**
  - **Previously shown to reduce HBV DNA, HBV RNA, HBsAg, HBeAg, & HBcrAg [1,2]**
- **Multiple triggers to avoid resistance development and increase coverage of viral genomes**

2 Targeted RNAi Molecules



HBV Transcript Map



[1] Gane et al. 2018 Hepatology 68:6 LB-25 [2] Gane et al. 2019 APASL Abstract 638

Study design AROHBV1001

- AROHBV1001 is a double blind, single dose escalating study in healthy volunteers and open label, multi-dose escalating study in patients with CHB
- The ongoing phase 2 portion of AROHBV1001 assesses 3 subcutaneous doses of JNJ-3989 administered weekly to monthly in HBeAg positive or negative CHB patients concomitantly with ETV or TDF
- This interim analysis reports reductions in HBsAg levels and safety in initial CHB cohorts
  - Reductions in HBsAg below certain thresholds in patients that had **24 weeks or more** of HBsAg assay results (n=40)
  - Effect of more frequent dosing (every other week or weekly) vs. monthly dosing (n=40)
  - Safety and tolerability (includes all CHB patients in cohorts 2b-11, n=56)

Baseline characteristics of CHB patients with ≥ 24 weeks of results available

Cohort	2b	3b	4b	5b	8	9	6	7	10	11	Total
Dose (mg)	100	200	300	400	300	300	100	100	200	300	
Dosing frequency	Q4w x 3						Q2w x 3	Q1w x 3			
Number CHB in cohort	4	4	4	4	4	4	4	4	4	4	40
HBeAg pos / HBeAg neg	1/3	0/4	1/3	1/3	4/0	4/0	0/4	1/3	1/3	0/4	13/27
NUC experienced	2	4	4	4	0	4	4	3	2	3	30
Race (Asian/Pacific Islander/Other)	4/0/0	4/0/0	4/0/0	4/0/0	3/1/0	4/0/0	3/1/0	1/3/0	4/0/0	3/0/1	34/5/1
Genotype (B/C/D/Unknown)	2/0/0/2	0/0/0/4	0/0/0/4	0/0/0/4	2/2/0/0	0/0/0/4	0/0/0/4	0/0/0/4	2/1/0/1	1/0/1/2	7/3/1/29
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)	1,115 (795)	1,573 (429)	7,613 (7,068)	3,564 (1,843)	16,435 (10,120)

- **Monthly dosing**
- **Mostly HBeAg negative**
- **Mostly NUC experienced**

- **Monthly dosing**
- **HBeAg positive**
- **Nuc experienced or naïve**

- **Shorter dosing intervals**
- **Every other week or weekly**
- **Mostly HBeAg negative**
- **Mostly NUC experienced**

- **Mean Baseline HBsAg**

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Safety and Tolerability

- 168 total doses administered to 56 CHB patients (cohorts 2b through 11)
- No drug related SAEs reported
  - Unrelated SAE of menorrhagia
  - Unrelated SAE of anxiety/depression
- All patients received all 3 scheduled doses; No dropouts
- No dose related pattern of adverse changes in laboratory values (e.g. ALT, AST, total bilirubin, creatinine)
- 17 total AEs at injection site (10% injections) reported (e.g. erythema, tenderness, bruising), all mild

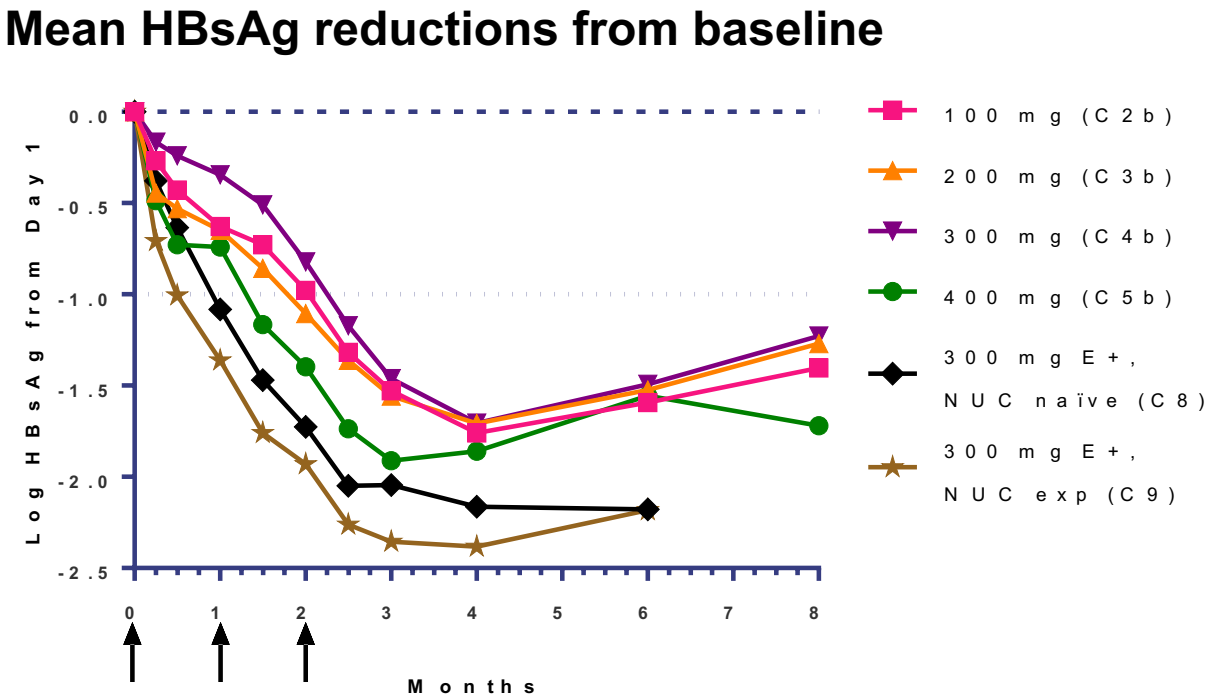
Adverse Events mostly mild without dose related pattern

AEs reported in ≥ 2 CHB patients

AROHBV1001 HBV Patients AE Reported Terms	Cohort 2b Open Label n = 8	Cohort 3b Open Label n = 8	Cohort 4b Open Label n =8	Cohort 5b Open Label n = 8	Cohort 6 Open Label n = 4	Cohort 7 Open Label n = 4	Cohort 8 Open Label n = 4	Cohort 9 Open Label n = 4	Cohort 10 Open Label n = 4	Cohort 11 Open Label n = 4	
Sore Throat, URTI	1	3	3	3	1	1	1	1	2	1	17
Injection Site Erythema/Redness, Very mild Erythema, Injection Site Rash, Injection Site Hematoma/Bruising, IS Pain			3	2		2	2	1		2	12
Headache			2	1		1			1	1	6
Raised or Elevation in Creatine Kinase			2			2	1				5
Lower Back Ache/Pain			1			2	1				4
Acne, Facial Acne							2				2
Bronchitis, Viral Bronchitis						1			1		2
Diarrhea, Intermittent Diarrhea			1	1							2
Pain in abdomen, Intermittent Right Upper Quadrant Pain		1		1							2
Insect Bites ankles, Flea Bites neck	1		1								2
Dizzy, Light headedness	1									1	2
Hot flush				1					1		2
Presence of calcium oxalate crystals in urine		1				1					2
Dry cough				1	1						2
Elevated Blood Pressure, Worsening Hypertension								1		1	2
Other all single occurring terms:											**64 Total**

(as of 3/8/2019)

All patients receiving 3 monthly doses have achieved > 1 log reduction in HBsAg



- NADIR in HBsAg is reached around 4 months post start of therapy
- Duration of pharmacologic effect persisted for > 4 months after last dose

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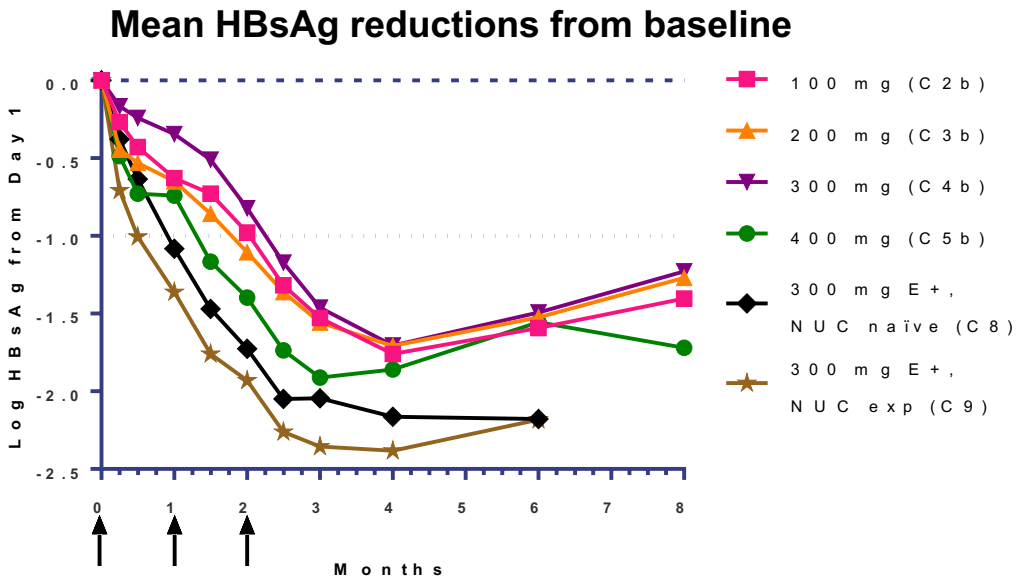
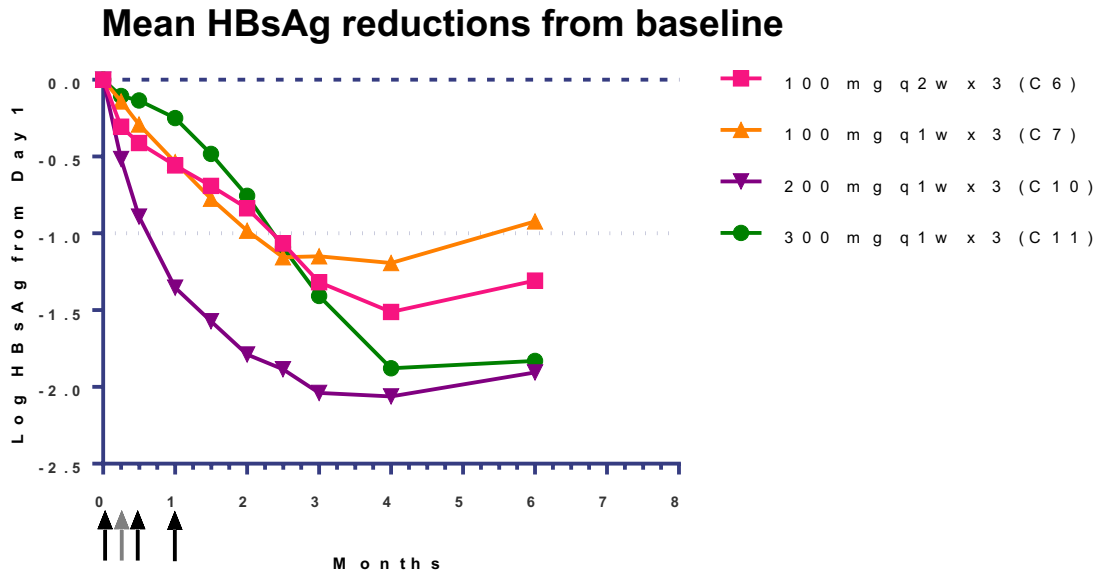
(as of 2/28/2019)

Shorter dosing intervals do not accelerate HBsAg decline

Monthly dosing intervals



Shorter dosing intervals



- Similar NADIR to monthly doses
- All HBsAg patients responded regardless of HBeAg status or previous NUC experience
  - Mean NADIR HBeAg negative (n=27): -1.82 Log10 IU/mL ± 0.09
  - Mean NADIR HBeAg positive (n=13): -2.28 Log10 IU/mL ± 0.21
  - 100% (40 of 40) had ≥ 1.0 Log10 IU/mL HBsAg reduction

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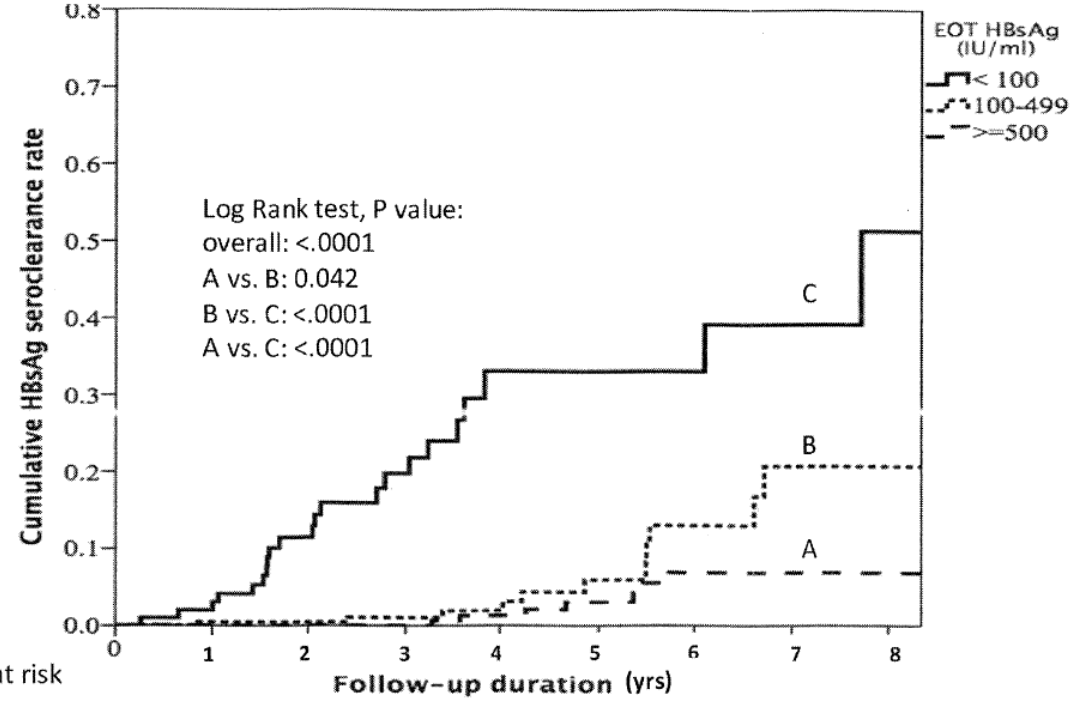
(as of 2/28/2019)

Topic of discussion: Is on-treatment HBsAg level important for HBsAg seroclearance?



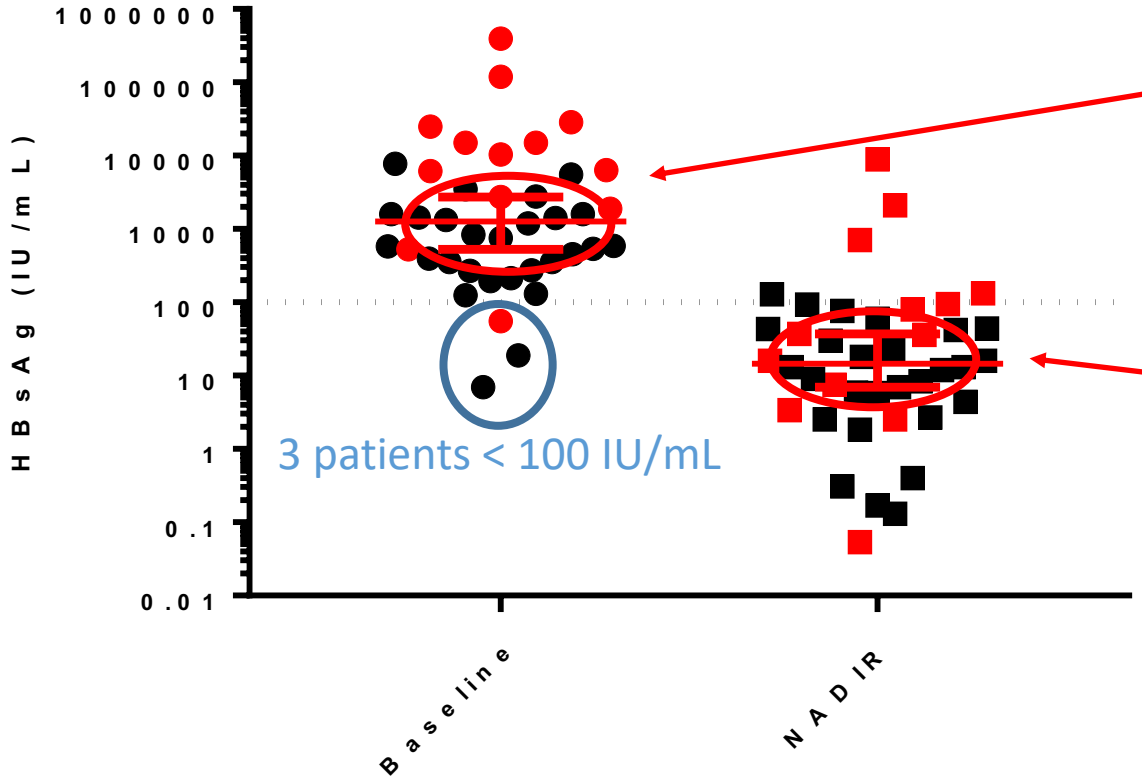
Patient at risk

	EOT HBsAg (IU/ml)									
A	>=500	303	92	61	39	17	14	12	8	4
B	100-499	274	232	185	129	86	52	30	18	8
C	<100	114	92	61	39	17	13	12	8	4

HBsAg levels of <100 IU/mL and HBsAg reduction of > 1 Log10 IU/mL have been associated with increased probability of HBsAg seroclearance after cessation of NUCs in HBeAg negative patients [1]

[1] Jeng et al. 2018 Hepatology 68:425-434

Distribution of quantitative HBsAg pre and post 3 doses of JNJ-3989



Baseline

Median: 1263 IU/mL
Min: 7.0 IU/mL
Max: 392,800 IU/mL

NADIR

Median: 14.5 IU/mL
Min: 0.05 IU/mL
Max: 8950 IU/mL

Red Points: HBeAg positive patients
Black Points: HBeAg negative patients

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Most patients (88%) achieve HBsAg ≤ 100 IU/mL after 3 doses of JNJ-3989

Baseline HBsAg		
Threshold	N	Percent
>1000 IU/mL	21 of 40	51%
>100 IU/mL	37 of 40	93%
NADIR HBsAg		
Threshold	N	Percent
≤100 IU/mL	35 of 40	88%
≤10 IU/mL	17 of 40	43%
≤1 IU/mL	5 of 40	13%

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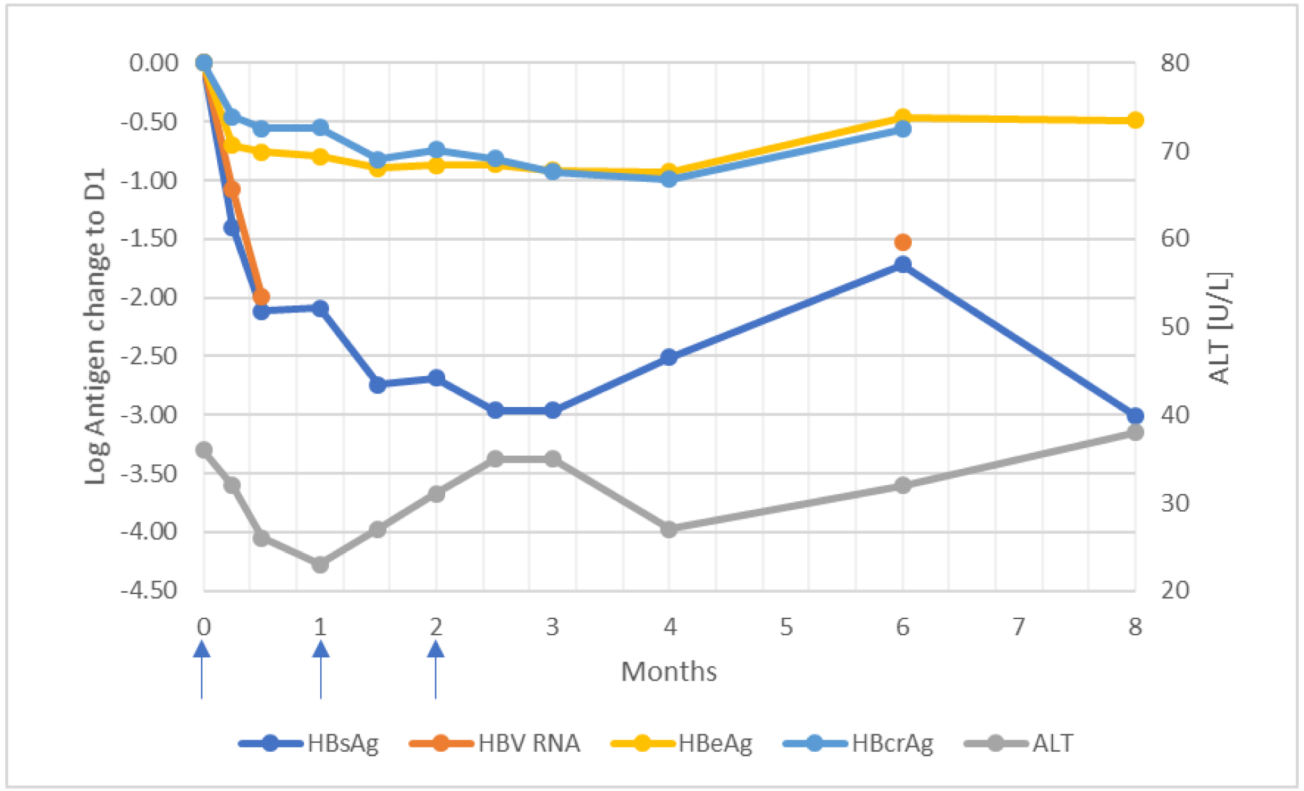
HBeAg positive patient with post-treatment antigen elevations followed by host response



- Male patient on ETV for 11 years and continued ETV throughout study
  - HBV DNA BLOQ throughout the study
- Patient received 400mg JNJ-3989 q4w x 3
- 3.0 Log10 HBsAg reduction from baseline with recovery beginning 2 mos after last dose
- 2.0 Log10 HBV RNA reduction to LLOQ
- 1.0 Log10 HBcrAg and 0.8 Log10 HBeAg reduction
- HBsAg decrease 6 months after last dose following attempted viral return consistent with increased host control of HBV virus (0.054 IU/mL) at 8 months

Summary and Conclusions

- JNJ-3989 (formerly ARO-HBV) administered subcutaneously was well tolerated at doses up to 400 mg
- RNAi with JNJ-3989 reduced all measurable viral products, including HBsAg in HBeAg positive or HBeAg negative patients
- JNJ-3989 rapidly reduces HBsAg to thresholds possibly associated with improved chances of HBsAg seroclearance in many patients, even after only 3 doses
  - 88% of patients achieved HBsAg <100 IU/mL
  - 100% of patients achieved ≥ 1.0 Log10 IU/mL HBsAg reduction

JNJ-3989 exhibits characteristics desirable for a cornerstone therapy in finite regimens aimed at HBsAg seroclearance in patients with chronic hepatitis B infection

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