AROHBV1001 Results Update

The Search for HBV/HDV Cure: Analyst Day at AASLD 2018

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Disclosures

- Dr. Given is an employee and shareholder in Arrowhead Pharmaceuticals, Inc.

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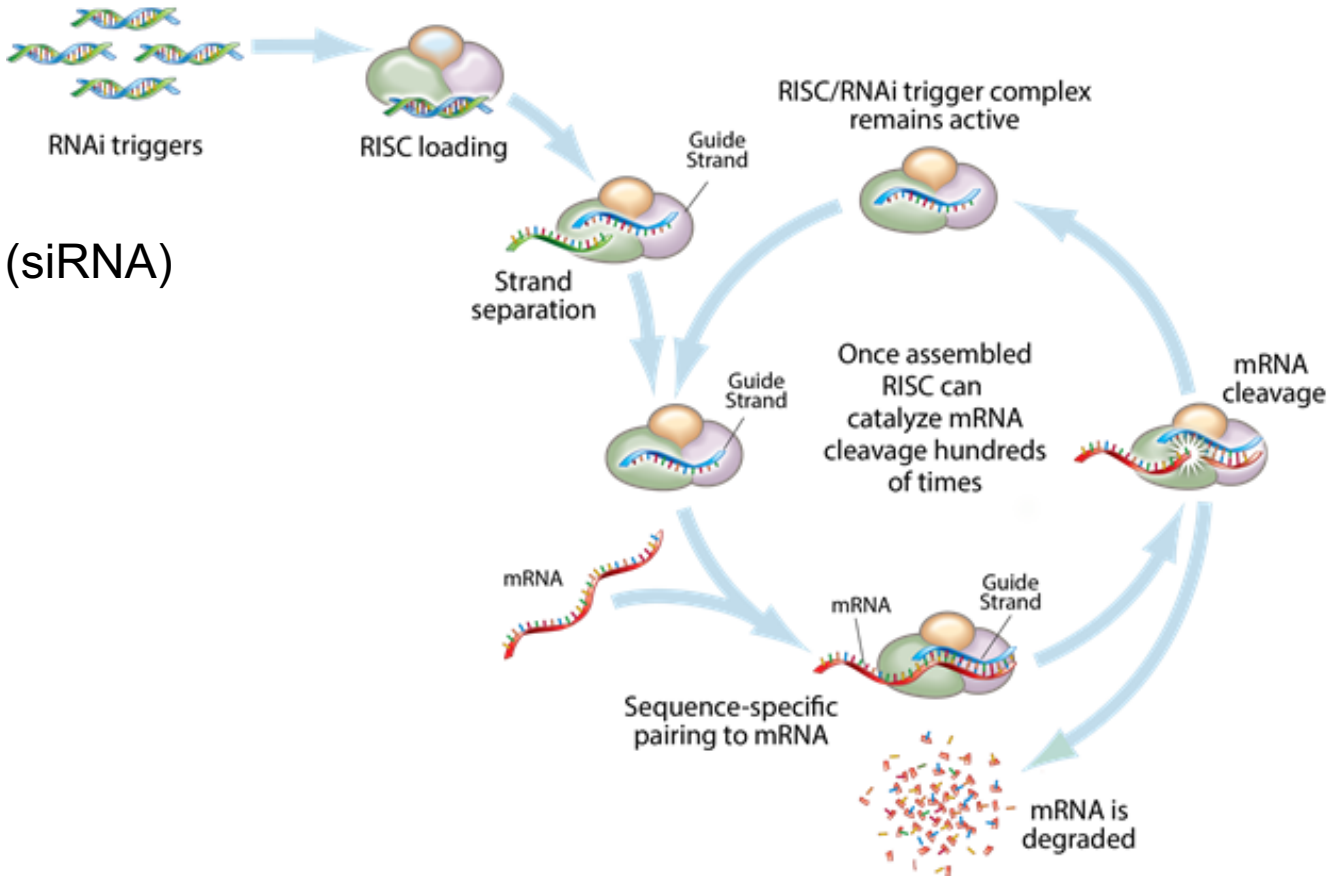
RNAi: Target the Gene Silence the Disease



Therapeutic gene silencing with **RNA interference** is highly precise and efficient

ARO-HBV: Key Design Elements

- Subcutaneous dosing, monthly or less frequent
- No need for active endosomal escape agent
- **Addresses full HBV transcriptome**
  - **Works for cccDNA *and* integrated-derived transcripts**
- Multiple triggers to avoid resistance development
- Powerful HBsAg reduction
- Wide therapeutic index
- Efficacy and safety in HBV patients

ARO-HBV Phase 1/2 Data Included in this Interim Update

- All NHV single dose data through day 29 EOS
- All CHB data of patients that
  - Received monthly doses x 3 (cohorts 2b-5b, 8, 9)

    AND
  - Had > 6 weeks of HBsAg response data available (n=24)

ARO-HBV Phase 1/2 study ongoing

NHV Cohorts

- Fully enrolled with 30 subjects
- All through Day 29 EOS visit
- **Now unblinded**

Healthy Volunteers (double blind) *			CHB Patients (open label)	
Cohort	Dose (Day 1)	Day 8 safety evaluation	Cohort	Dose Regimen
Cohort 1	35 mg		N/A	N/A
Cohort 2	100 mg		Cohort 2b (all eligible CHB patients regardless of NUC or HBeAg status)	100 mg dosed on Day 1, 29, 57
Cohort 3	200 mg		Cohort 3b (all eligible CHB patients regardless of NUC or HBeAg status)	200 mg dosed on Day 1, 29, 57
Cohort 4	300 mg		Cohort 4b (all eligible CHB patients regardless of NUC or HBeAg status)	300 mg dosed on Day 1, 29, 57
Cohort 5	400 mg		Cohort 5b (all eligible CHB patients regardless of NUC or HBeAg status)	400 mg dosed on Day 1, 29, 57
			Cohort 6 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 15, 29
			Cohort 7 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 8, 15
			Cohort 8 HBeAg+, treatment naïve	Dose TBD** Day 1, 29, 57
			Cohort 9 HBeAg+, entecavir or tenofovir experienced	Dose TBD** Day 1, 29, 57
			Cohort 10 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 8, 15
			Cohort 11 (all eligible CHB patients regardless of NUC or HBeAg status)	Dose TBD** Day 1, 8, 15

NHV Safety Summary

- 20 active : 10 placebo
- No serious AEs, no dropouts
- No pattern of adverse changes in laboratory values (e.g. ALT, AST, Total Bilirubin, Creatinine)
- Subjects reporting AE at injection site: 1 mild bruise at injection site, 1 mild tenderness at injection site

NHV Unblinded AE Table

AEs in >1 subject (as of 8/9/2018)

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

- Most common AE: Headache (35% active)
- 70% active v 80% PBO reporting at least 1 AE

ARO-HBV Phase 1/2 Study Update

Healthy Volunteers (double blind) *			CHB Patients (open label)	
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CHB Cohorts

- Fully enrolled per original protocol and per amendment adding cohorts 10 and 11.

- Latest protocol amendments (approved in AU, NZ, HK):
  - 2b-5b up to 8 per cohort
  - 1 year of follow up post-last dose
  - Cellular immunology evaluation in NZ only (U. of Auckland)
  - Adding cohort 1b (25 mg), 1c (50mg) pending EC approval

- TBD doses
  - Cohort 6: 100mg QoWk
  - Cohort 7: 100mg QWk
  - **Cohorts 8, 9 (e+): 300mg Q28 day**
  - Cohort 10: 200mg Qwk
  - Cohort 11: 300mg Qwk

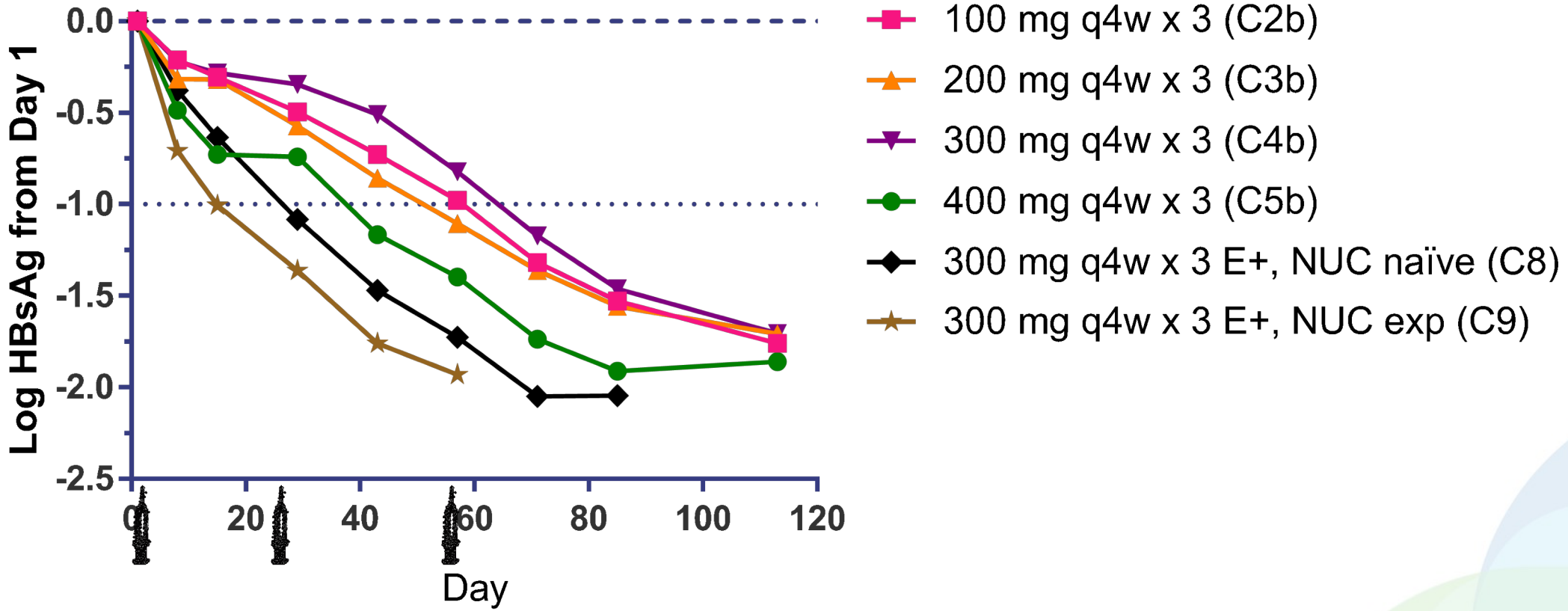
CHB Safety Summary

- 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

CHB Patient AEs in > 1 Subject (as of 10/23/18)

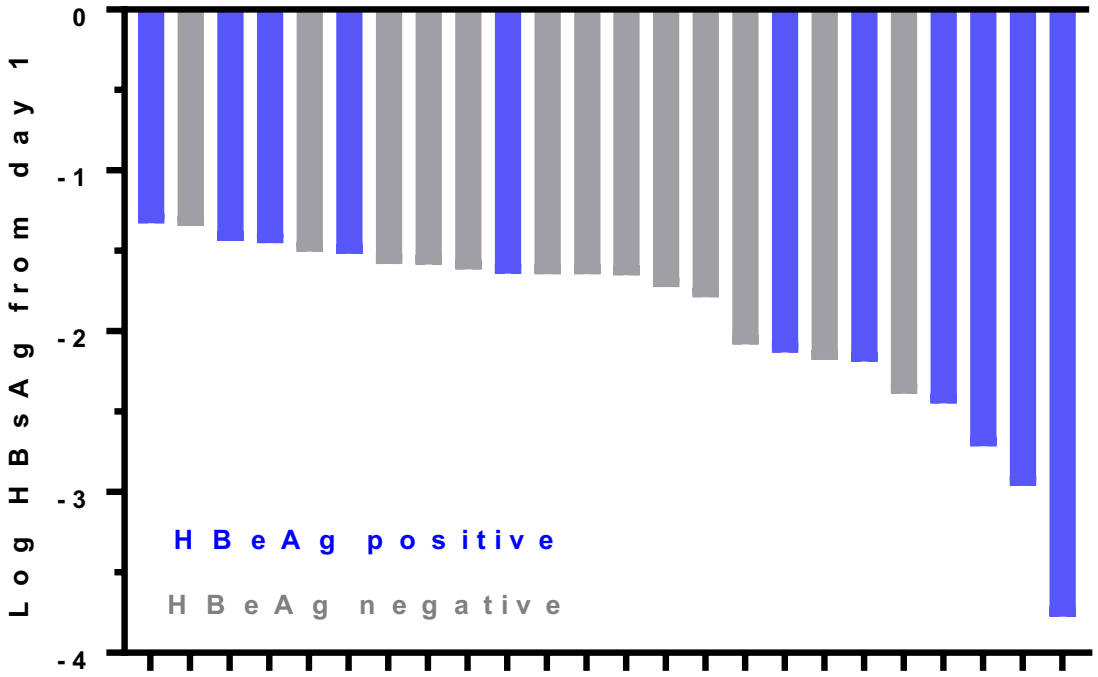
AEs in HBV Patients	Cohort 2b 100 mg	Cohort 3b 200 mg	Cohort 4b 300 mg	Cohort 5b 400 mg	Cohort 8 300 mg	Cohort 9 300 mg	Total AEs n=24
AE Reported Terms	AROHBV n = 4	AROHBV n = 4	AROHBV n = 4	AROHBV n = 4	AROHBV n = 4	AROHBV n= 4	
Insect bites	1		1				2
Upper respiratory infection, sore throat	1		1		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

Mean Log HBsAg Reductions by Cohort



Previously reported 4 log reduction in 100 mg patient reduced to 2 logs on re-assay

Individual Max Log HBsAg Reduction from Day 1



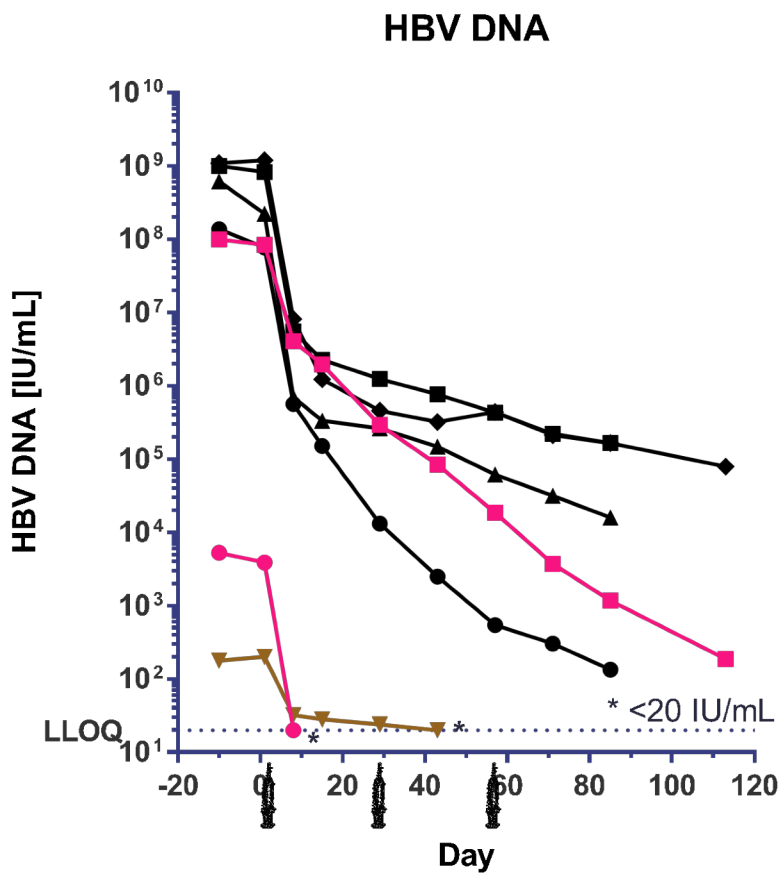
- All patients with > 6 weeks of HBsAg results (n=24)
- Range of NADIR: -1.3 to -3.8 Log_{10}
- Mean NADIR: -1.9 Log_{10}
- Similar responses observed for HBeAg negative and positive patients
  - HBeAg positive (n=11): - 2.1 Log10
  - HBeAg negative (n=13): -1.8 Log10

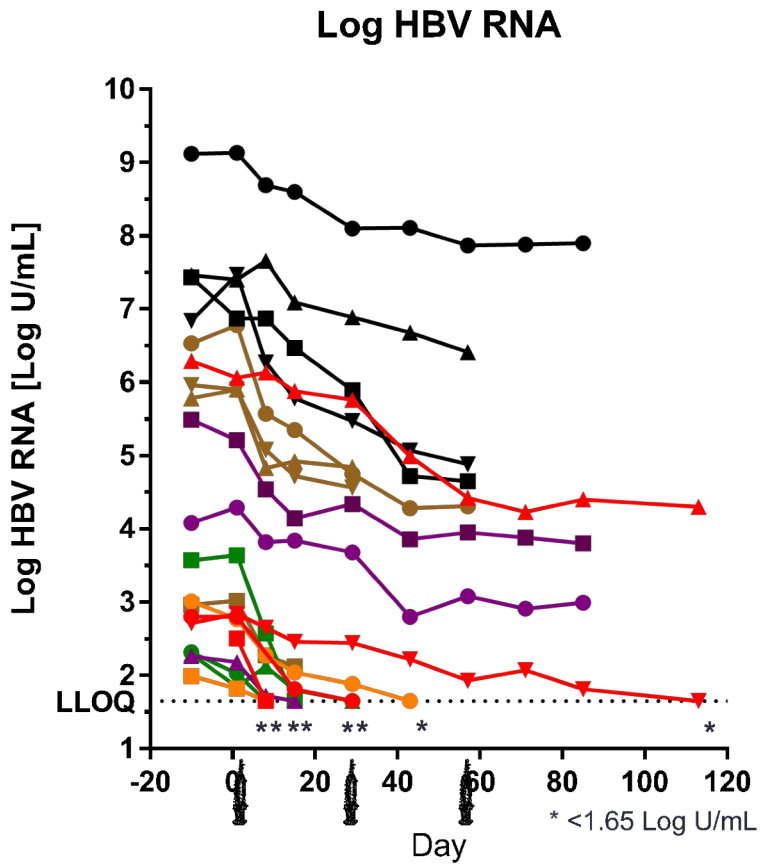
Nadir HBsAg Responses for Monthly Dosed Patients with at least 6 Weeks or Exposure

Exposure of 6 weeks or more (n= 24)

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

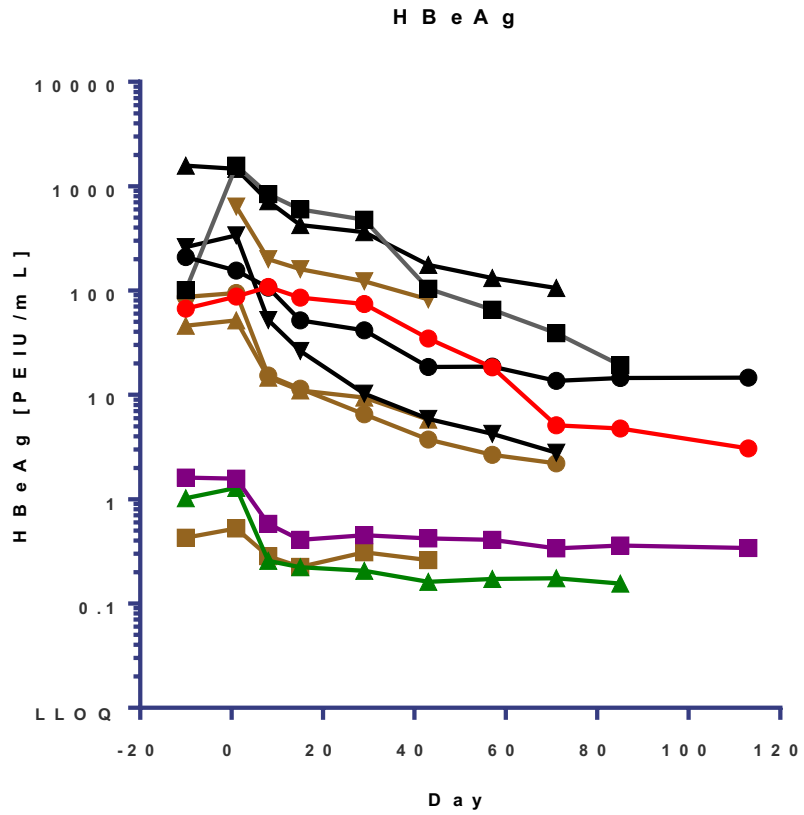
Individual HBV DNA and RNA Responding Well

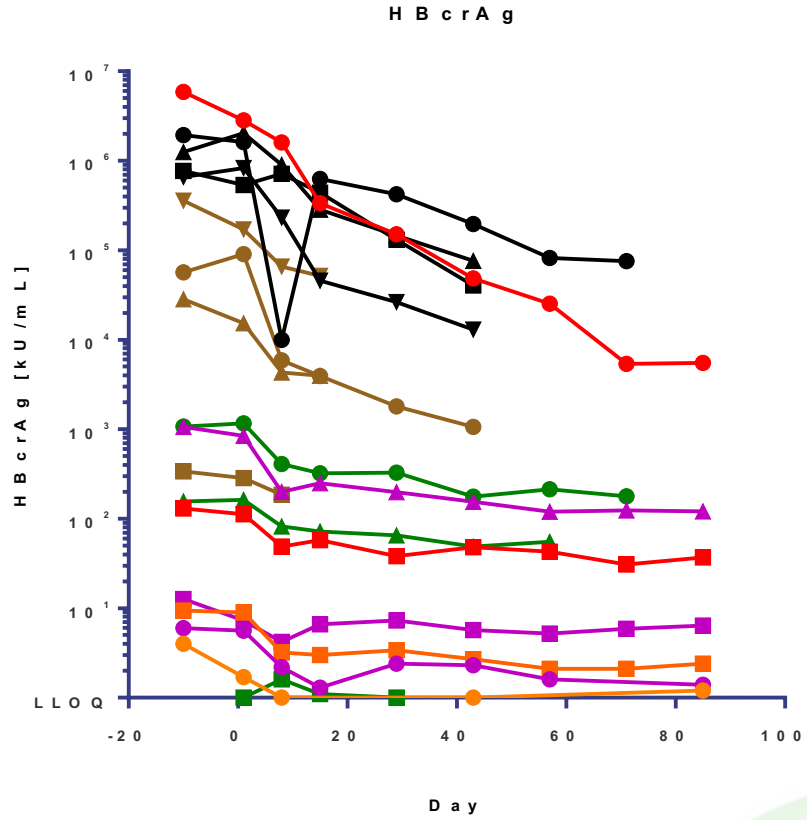




Colors in graphs indicate cohorts as follows: Red (C2b), orange (C3b), purple (C4b), green (C5b), black (C8), brown (C9)

Individual HBeAg and HBcrAg Also Showing Response





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Early Conclusions for ARO-HBV

- ARO-HBV appears to be well tolerated
- Responses generally slower in absence of endosomal escape (not unique to HBV)
- **HBsAg responding to ARO-HBV in all patient populations (HBeAg +/-, NUC +/-)**
- Responses increasing with each dose in most patients
- HBeAg, HBV RNA, HBcrAg, HBV DNA all showing response

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