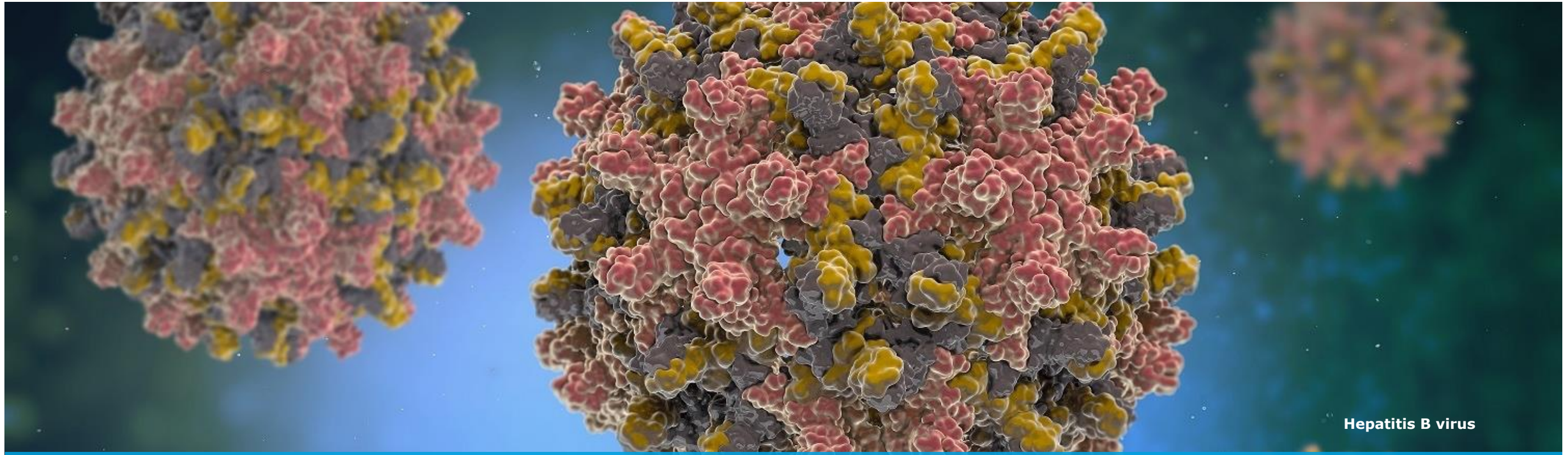

Short interfering RNA JNJ-3989 combination therapy in chronic hepatitis B shows potent reduction of all viral markers but no correlate was identified for HBsAg reduction and baseline factors

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Disclosures for all authors

- **EG** has been an advisor and/or speaker for AbbVie, Aligos, Arbutus, Arrowhead, Assembly, Avalia, Clear B Therapeutics, Dicerna, DrugFarm, Enanta, Finch Therapeutics, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Novartis, Roche and Vir Bio.
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- **M-FY** serves as advisor/consultant for AbbVie, Arbutus Biopharma, Allovir International Bristol Myer Squibb, Clear B Therapeutics, Dicerna Pharmaceuticals, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, Roche and Springbank Pharmaceuticals, and receives grant/research support from Assembly Biosciences, Arrowhead Pharmaceuticals, Bristol Myer Squibb, Fujirebio Incorporation, Gilead Sciences, Merck Sharp and Dohme, Roche, Springbank Pharmaceuticals and Sysmex Corporation
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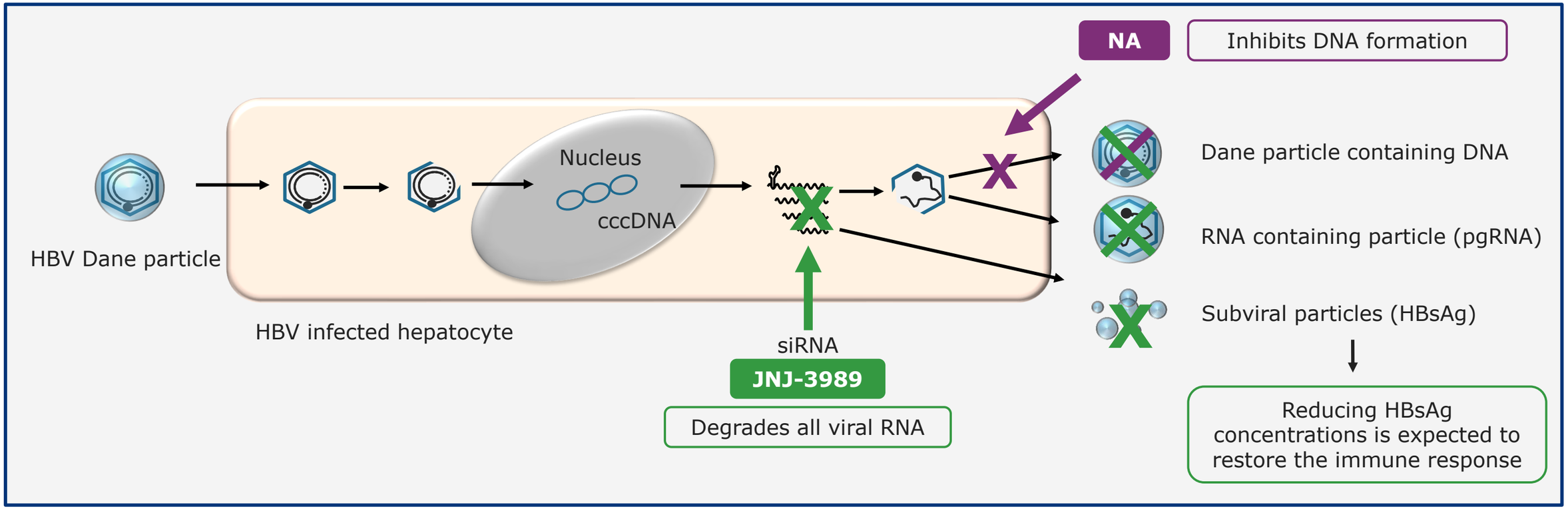
JNJ-3989: Mechanisms of action



- NAs inhibit viral replication but **do not prevent the production of HBsAg**
- In AROHBV1001, JNJ-3989 (**100–400 mg; 3 monthly injections**) in combination with NA (TDF or ETV) resulted in potent reduction of **HBsAg, HBeAg, HBV RNA and HBcrAg**, and was well tolerated in patients with CHB[1]
- The effects were sustained in 38% of patients until **Day 392** (336 days after last dose of JNJ-3989) with a mean (SE) HBsAg reduction of 1.96 (0.20) $\log_{10}$ IU/mL in patients with "sustained" response*[1]

1. Gane et al. EASL 2020. Oral presentation GS10. Sustained response was defined as a >1 $\log_{10}$ IU/ml reduction in HBsAg from Day 0 through Day 392.
cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; ETV, entecavir; HBeAg, hepatitis B e antigen; HBcrAg, hepatitis B core related antigen; HBsAg, hepatitis B surface antigen; HBV RNA, hepatitis B virus RNA; NA, nucleos(t)ide analogue; pgRNA, pregenomic RNA; SE, standard error; siRNA, short interfering RNA; TDF, tenofovir disoproxil fumarate

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AROHBV1001: Objectives of analyses through Day 168

1. To assess the impact of baseline factors on HBsAg reduction during treatment with JNJ-3989 and NA

2. To compare the effect of JNJ-3989 and NA on HBsAg, HBeAg, HBcrAg and HBV RNA levels

HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV RNA, hepatitis B virus RNA; NA, nucleos(t)ide analogue

AROHBV1001: Study design

Cohorts receiving JNJ-3989 (100–400mg; 3 x Q4W) + NA

Study population:

1. CHB HBeAg-positive or -negative patients
2. NA-experienced or -naïve patients

Dose administration:

- Injections (sc) of JNJ-3989 were given on Days 0, 28 and 56
- Oral QD treatment with TDF or ETV was started or continued on Day 0 and was administered throughout the study

CHB, chronic hepatitis B; ETV, entecavir; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analogue; Q4w, every 4 weeks; QD, once daily; sc, subcutaneous; TDF, tenofovir disoproxil fumarate

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AROHBV1001: Baseline characteristics and demographics

Baseline patient characteristics of the JNJ-3989 3 x Q4W 100–400 mg cohort	
Baseline Characteristics	**Number of patients (N=40)**
Age, years; median (range)	45 (26–66)
Male, n (%)	29 (72.5)
Race, n (%)	
Asian	34 (85.0)
Caucasian	1 (2.5)
Other	5 (12.5)
NA-experienced, n (%)	32 (80.0)
HBeAg-positive, n (%)	14 (35.0)

Baseline levels of viral markers in the JNJ-3989 3 x Q4W 100–400 mg cohort*			
Viral maker	**HBeAg Status**	**N**	**Mean (SE)**
HBV DNA (log_{10} IU/mL)	Negative	3	2.7 (0.5)
	Positive	8	6.7 (0.9)
HBV RNA (log_{10} U/mL)	Negative	14	2.6 (0.2)
	Positive	14	6.3 (0.4)
HBcrAg (log_{10} kU/mL)	Negative	11	0.9 (0.2)
	Positive	14	4.8 (0.3)
HBeAg (log_{10} PEIU/mL)	Positive	14	1.7 (0.3)
HBsAg (log_{10} IU/mL)	Negative	26	2.7 (0.1)
	Positive	14	3.9 (0.2)

*Includes patients with viral marker concentrations >LLOQ.
HBeAg, hepatitis B e-antigen; HBcrAg, hepatitis B core related antigen; HBsAg, hepatitis B surface antigen; IU, international units; kU, kilo units; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; PEIU, Paul Erlich Institute Units; Q4W, every 4 weeks; SE, standard error

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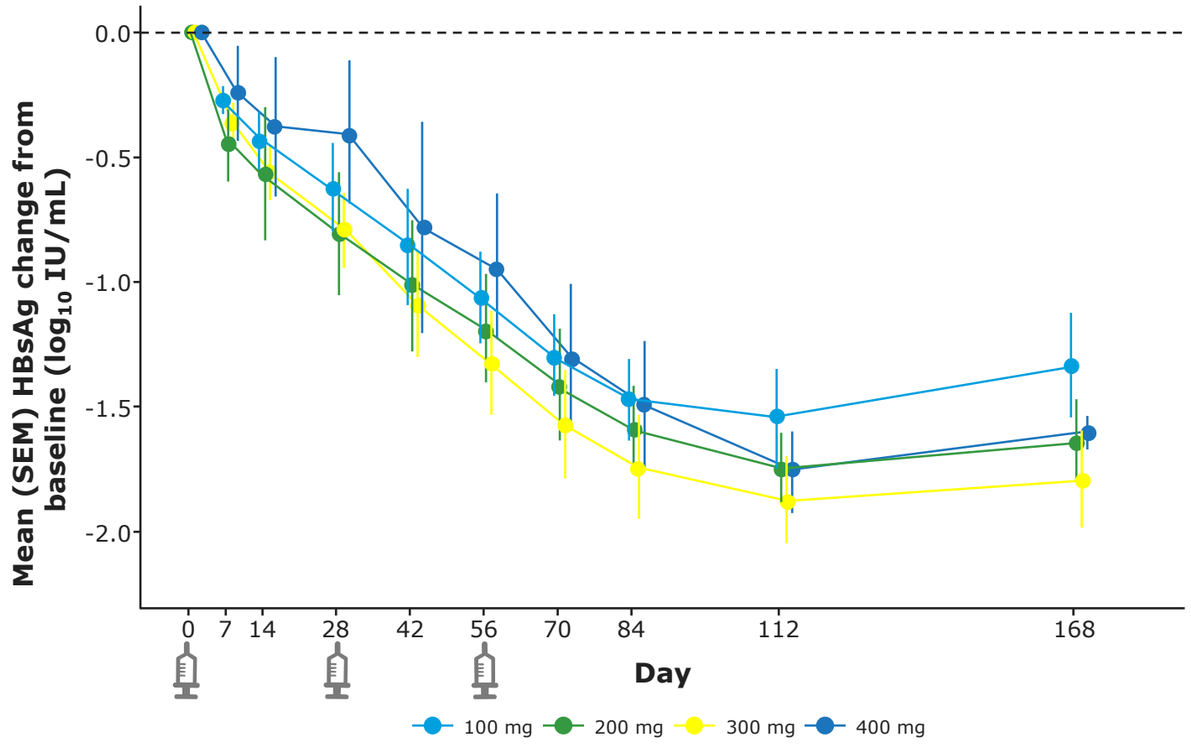
AROHBV1001: Effect of JNJ-3989 and NA treatment on reduction in HBsAg

Mean change in HBsAg from Day 0 to Day 168



- Mean (range) HBsAg reduction from baseline at nadir was 1.93 (0.73, 3.84) log_{10} IU/mL

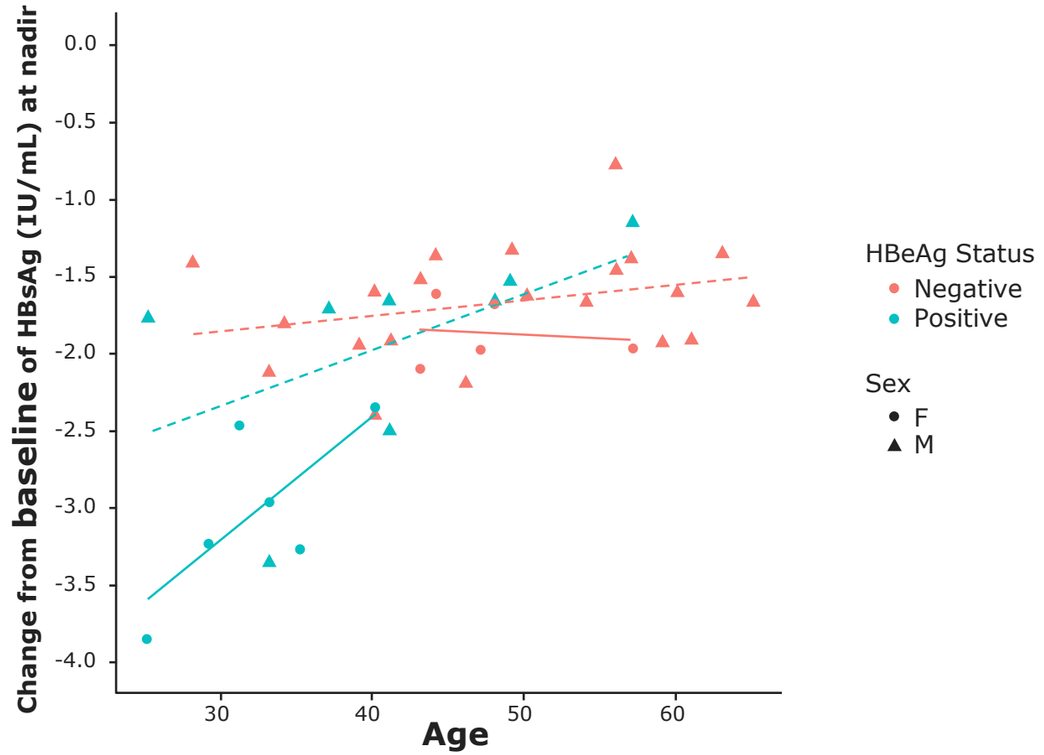
- 39/40 patients (98%) achieved >1 log_{10} IU/mL reduction at the nadir

Treatment with **JNJ-3989 and NA resulted in pronounced HBsAg reductions**

HBsAg, hepatitis B surface antigen; IU international unit; NA, nucleos(t)ide analogue; vir, virologically; surpr, suppressed

AROHBV1001: Effect of JNJ-3989 and NA treatment on reduction in HBsAg according to baseline characteristics

Relationship between age, gender and HBeAg status with maximum reduction in HBsAg from baseline



Maximum HBsAg reduction from baseline n/N (%)	<2 $\log_{10}$ IU/mL	≥2 $\log_{10}$ IU/mL
Overall	28/40 (70)	12/40 (30)
HBeAg^{+}	6/14 (43)	8/14 (57)
HBeAg^{-}	22/26 (85)	4/26 (15)
Female	4/11 (36)	7/11 (64)
Male	24/29 (83)	5/29 (17)
≤40 years old	6/15 (40)	9/15 (60)
>40 years old	22/25 (88)	3/25 (12)

Reductions in HBsAg were **more pronounced in HBeAg-positive patients compared with HBeAg-negative patients**

F, female; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; IU, international unit; M, male; NA, nucleos(t)ide analogue

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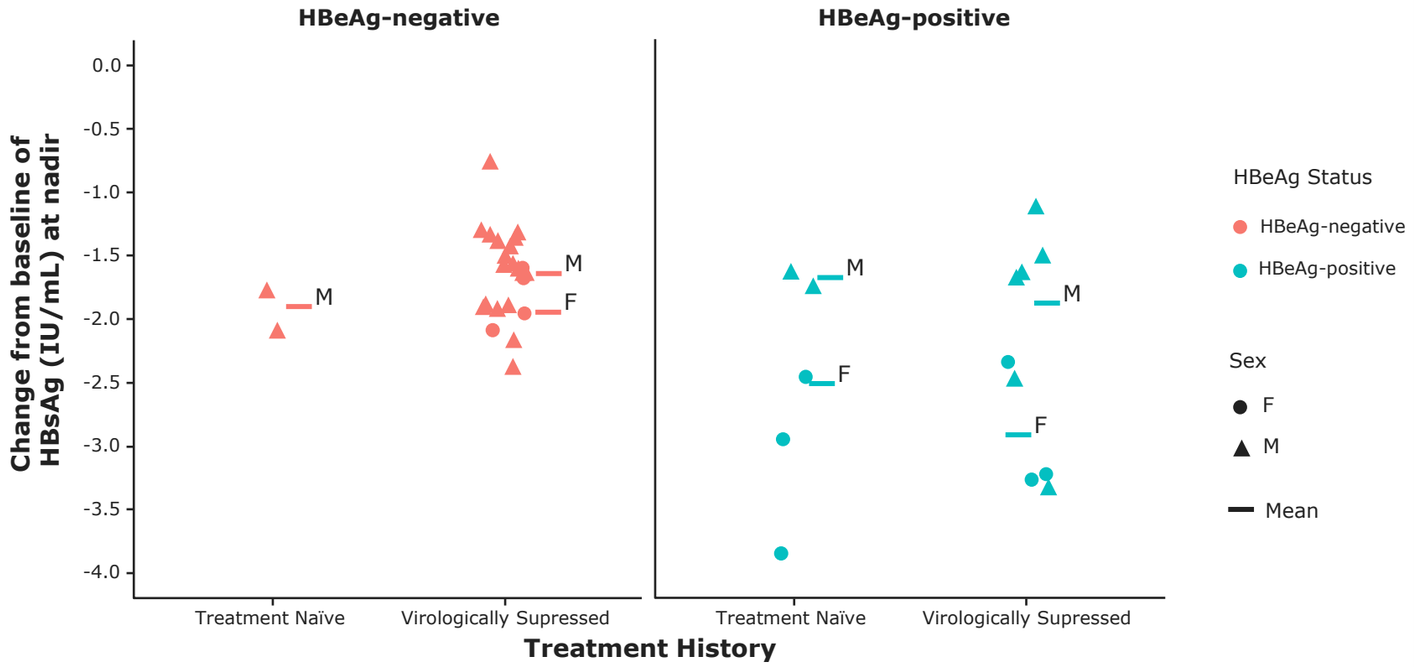
AROHBV1001: Effect of JNJ-3989 and NA treatment on reduction in HBsAg according to treatment history

Relationship between HBeAg status, gender, and treatment history with maximum reduction in HBsAg from baseline

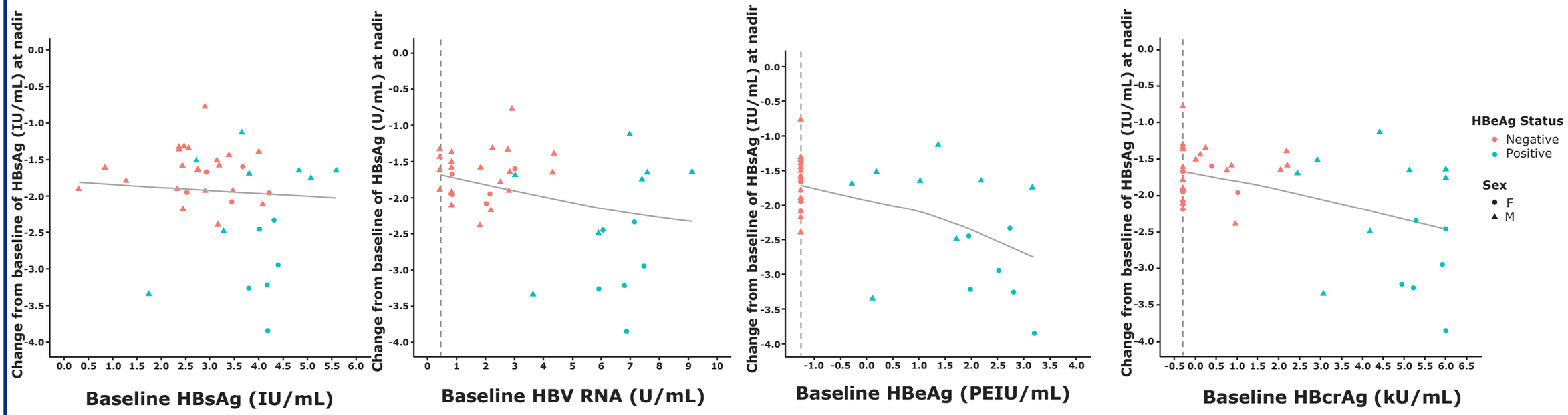


Treatment history was not associated with reductions in HBsAg

F, female; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; IU, international unit; M, male; NA, nucleos(t)ide analogue

AROHBV1001: Effect of JNJ-3989 and NA treatment on reduction in HBsAg according to baseline viral markers

Relationship between baseline viral markers and maximum reduction in HBsAg from baseline



Reduction in HBsAg was not associated with baseline HBsAg levels
Larger reductions in HBsAg were associated with higher levels of HBV RNA, HBeAg and HBcrAg at baseline

Dotted lines indicate negative samples. F, female; HBcrAg, hepatitis B core related antigen; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV RNA, hepatitis B virus RNA; IU, international unit; M, male; NA, nucleos(t)ide analogue; PEIU, Paul Erlich Institute Units

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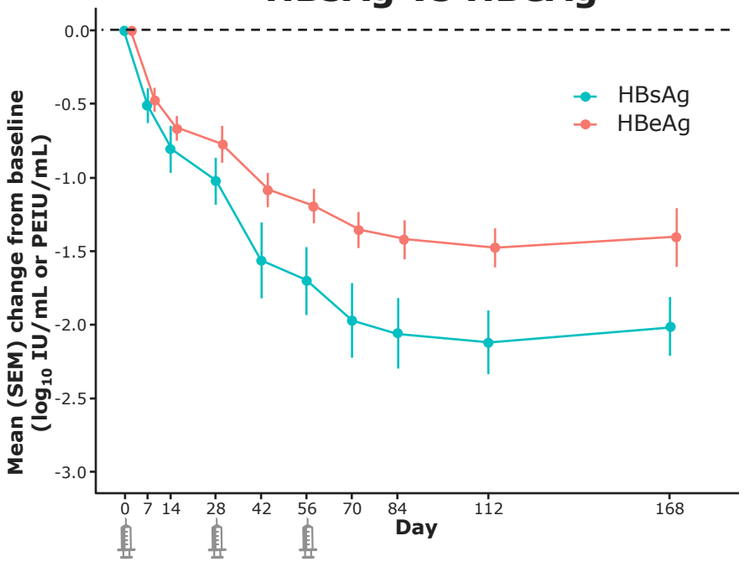
AROHBV1001: Effect of JNJ-3989 and NA treatment on reduction of all viral markers

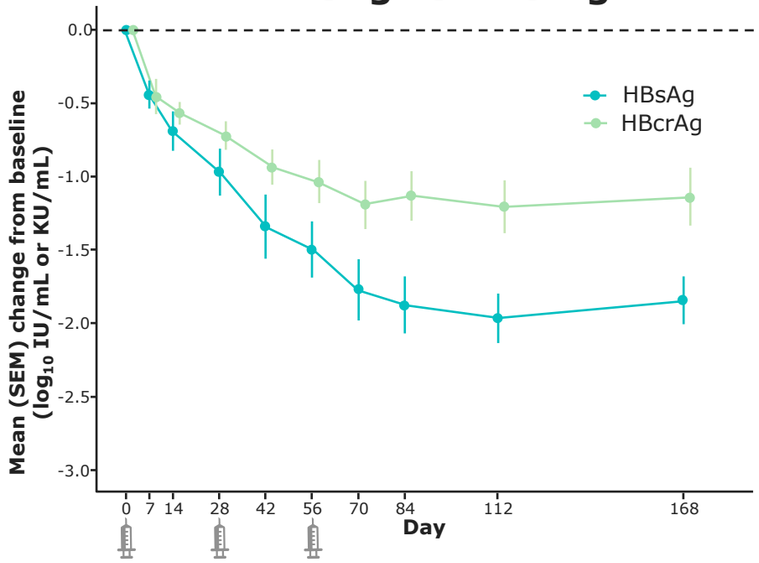
Mean change of viral markers, comparing HBsAg with HBeAg, HBcrAg and HBV RNA from Day 0 to Day 168 (N=40)*

HBsAg vs HBeAg



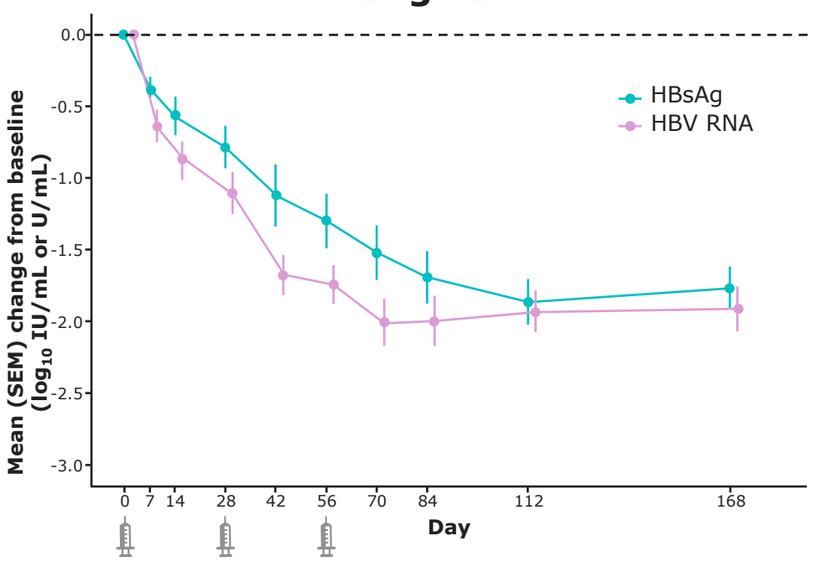
	Mean (SE); n change at Day 112
HBsAg, IU/mL	-2.11 (0.21); 12
HBeAg, PEIU/mL	-1.41 (0.12); 12

HBsAg vs HBcrAg



	Mean (SE); n change at Day 112
HBsAg, IU/mL	-1.97 (0.16); 18
HBcrAg, kU/mL	-1.20 (0.17); 18

HBsAg vs HBV RNA



	Mean (SE); n change at Day 112
HBsAg, IU/mL	-1.86 (0.15); 21
HBV RNA, U/mL	-1.93 (0.14); 21

Reductions in HBsAg and HBV RNA were generally more pronounced compared with HBeAg and HBcrAg

*Only patients with baseline levels of HBeAg, HBcrAg and HBV RNA levels >1 $\log_{10}$ IU/mL above LLOQ were included, respectively

HBcrAg, hepatitis B core related antigen; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV RNA, hepatitis B virus RNA; IU, international unit; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; PEIU, Paul Erlich Institute Units; SE, standard error

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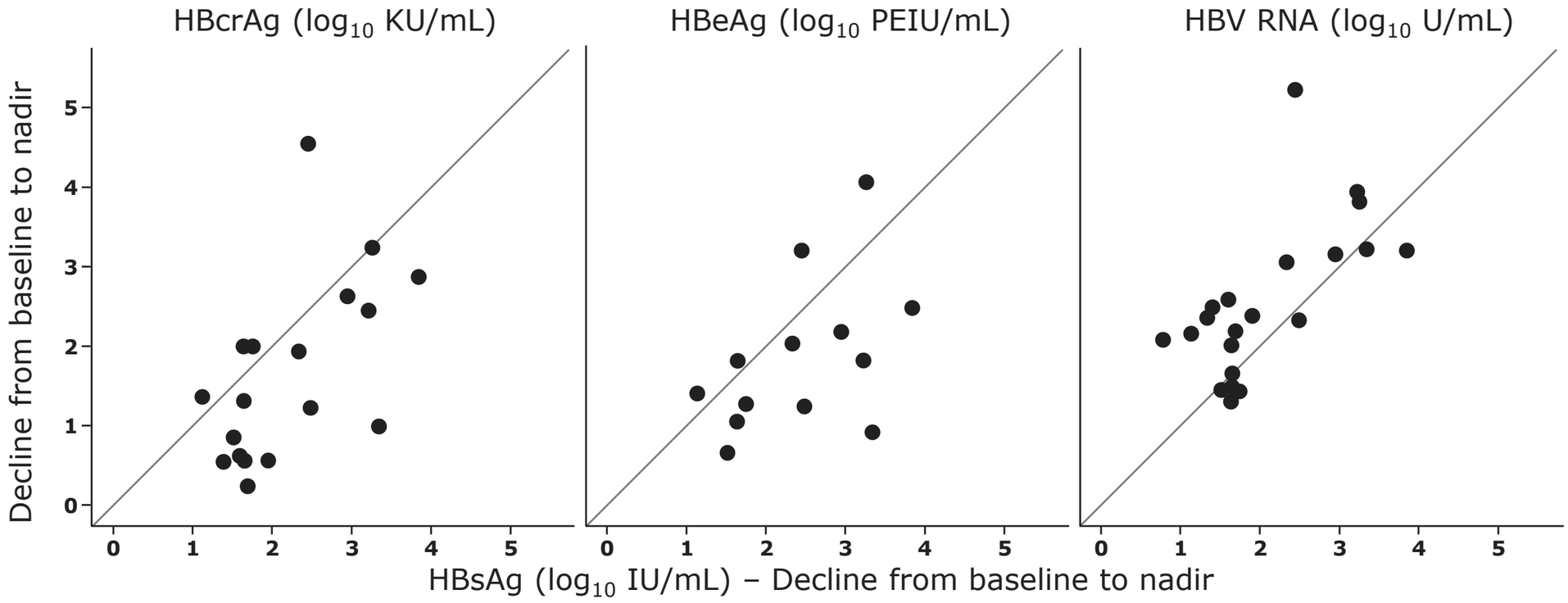
AROHBV1001: Effect of JNJ-3989 and NA treatment on reduction of viral markers for individual patients (1/2)

Correlation between maximum HBsAg decline and HBeAg, HBcrAg and HBV RNA from Day 0 for individual patients*



*Only patients with baseline levels of HBeAg, HBcrAg and HBV RNA levels >1 $\log_{10}$ above LLOQ were included

HBcrAg, hepatitis B core related antigen; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV RNA, hepatitis B virus RNA; IU, international unit; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue

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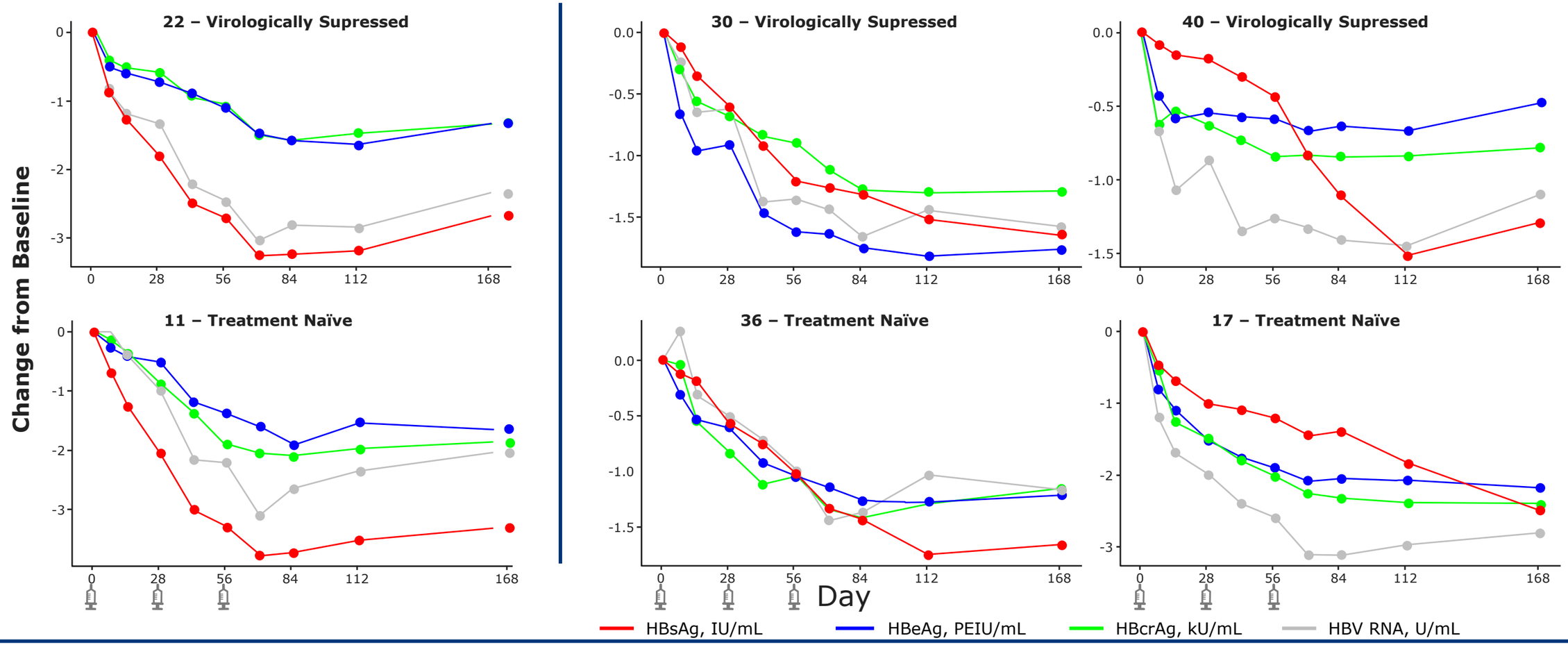
AROHBV1001: Effect of JNJ-3989 and NA treatment on reduction in viral markers for individual patients (2/2)

Change in viral markers for individual patients from Day 0 to Day 168



HBcrAg, hepatitis B core related antigen; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV RNA, hepatitis B virus RNA; IU, international units; NA, nucleos(t)ide analogue; PEIU, Paul Erlich Institute Units

AROHBV1001: Conclusions

Treatment with JNJ-3989 (100–400mg, Q4W) in combination with NA resulted in **sustained reductions of all viral markers** HBsAg, HBeAg, HBcrAg and HBV RNA

Treatment with JNJ-3989 (100–400mg, Q4W) and an NA was associated with greater HBsAg reductions in:

- HBeAg-positive patients
- Patients with higher levels of HBV RNA, HBeAg and HBcrAg at baseline

Reductions in HBsAg and HBV RNA were more pronounced compared with HBeAg and HBcrAg

These findings are being evaluated in larger Phase 2b studies

CHB, chronic hepatitis B; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV RNA, hepatitis B virus RNA; NA, nucleos(t)ide analogue; Q4w, every 4 weeks

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