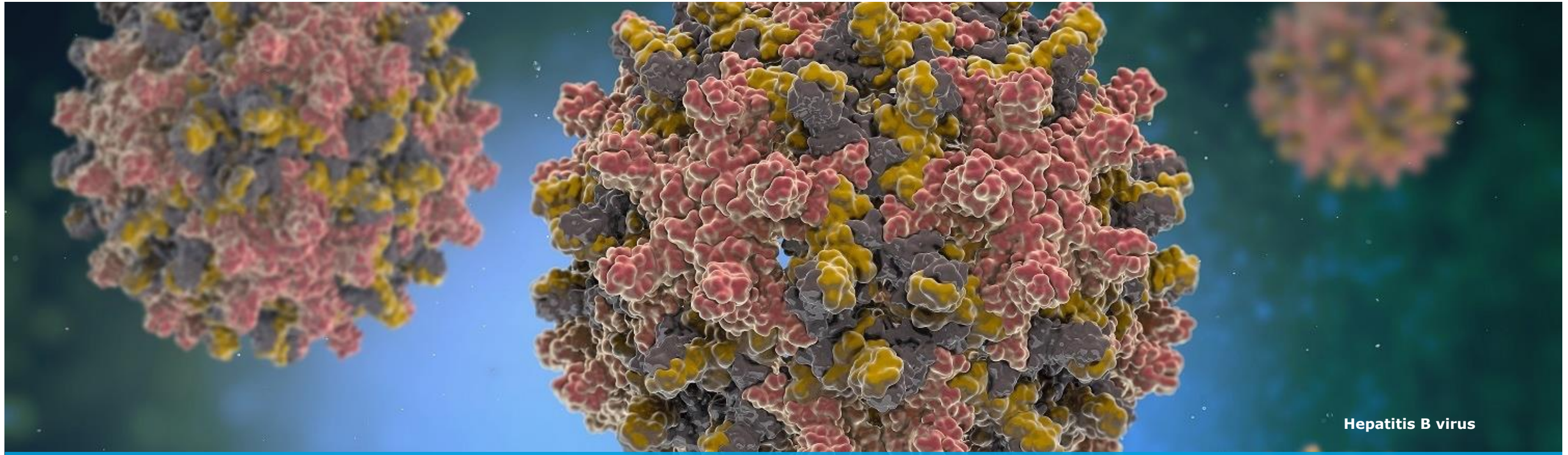


Short-term treatment with RNA interference therapy, JNJ-3989, results in sustained hepatitis B surface antigen suppression in patients with chronic hepatitis B receiving nucleos(t)ide analogue treatment

Edward Gane[1], Stephen Locarnini[2], Tien Huey Lim[3], Simone Strasser[4], William Sievert[5], Wendy Cheng[6,7], Alex Thompson[8], Bruce Given[9], Thomas Schluep[9], James Hamilton[9], Michael Biermer[10], Ronald Kalmeijer[11], Maria Beumont[11], Oliver Lenz[10],Gavin Cloherty[12], Danny Ka-Ho Wong[13], Christian Schwabe[1], Kathy Jackson[2], Carlo Ferrari[14], Ching Lung Lai[13], Robert G. Gish[15], Man-Fung Yuen[13]

[1]Auckland Clinical Studies, Auckland, New Zealand; [2]Victorian Infectious Diseases 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]Janssen Pharmaceuticals BV, Beerse, Belgium; [11]Janssen R&D, Titusville, NJ, USA; [12]Abbott Diagnostics, Abbott Park, IL, USA; [13]The University of Hong Kong, Hong Kong, China; [14]University of Parma, Parma, Italy; [15]Hepatitis B Foundation, Doylestown, PA, USA

Janssen Infectious Diseases & Vaccines

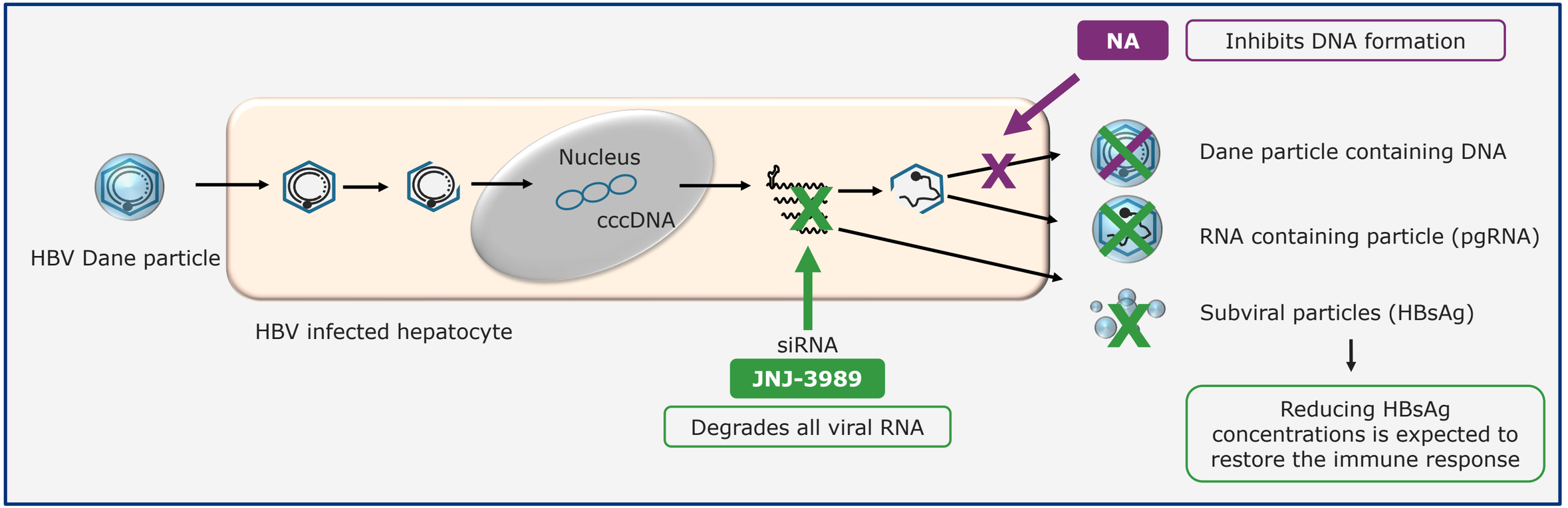
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Disclosures for all authors

- **EG** has been an advisor and/or speaker for AbbVie, Arrowhead, Assembly, Gilead, GSK, Janssen, Merck, Novartis, Roche and Vir Bio.
- **SL** receives consulting fees from Roche Molecular, AusBio Ltd, Janssen, Abbvie and Clear-B, and contract research grants from Spring Bank Pharmaceuticals, Inc. and Clear-B.
- **SS** has received honoraria for advisory boards or speaker fees from Gilead, BMS, AbbVie, MSD, Bayer, Eisai, Ipsen, Pfizer and CSL.
- **AT** has served on advisory boards for Gilead, Abbvie, Merck, BMS, Bayer and Eisai, has received speaker fees from Gilead, Abbvie, Merck and BMS, and has received institutional research grants from Gilead, Abbvie and Merck.
- **BG, TS,** and **JH** are employees of Arrowhead.
- **MB, RK, MB,** and **OL** are employees of Janssen Pharmaceuticals and may be Johnson & Johnson stockholders.
- **GC** is an Abbott employee and shareholder.
- **CS** has provided advice to Johnson & Johnson and Vir Biotechnology.
- **CF** is an advisory board member for Gilead, Roche, MSD, Abbvie, BMS and Vir, a consultant for Gilead, Arrowhead, Abbvie, Humabs (Ch), Abivax and Transgene, and receives research grants from Gilead, Roche, Abbvie and Bristol Myer Squibb.
- **CLL** discloses sponsored lectures for Gilead Sciences
- **RGG** had grants/research support from Gilead is/has been a consultant and/or advisor to Abbot, Abbvie, Access Biologicals, Antios, Arena, Arrowhead, Bayer AG, Bristol Myers Squibb, Dova, Dynavax, Eiger, Eisai, Enyo, eStudySite, Exelixis, Forty-Seven Inc, Genlantis, Gerson Lehrmann Group, Gilead Sciences, HepaTX, HepQuant, Intercept, Ionis, Janssen, Laboratory for Advanced Medicine, Lilly, Merck, Salix, Shionogi, Spring Bank, and Viking Therapeutics, hold positions on scientific or clinical advisory boards for: Abbott, AbbVie, Merck, Arrowhead, Bayer, Dova Pharmaceuticals, Eiger, Enyo, Hatch Biofund, HepQuant, Intercept, Jansen, Medimmune is an advisory consultant for Biocollections, Fujifilm/Wako, and Quest, is on the data safety monitoring board for Ionis, and Eiger, has consultant confidentiality agreements with: Abbot, Abbvie, Access Biologicals, ADMA Biologics, AEC Partners, Aligos Therapeutics, Arena Pharmaceuticals, Arrowhead, Arterys Inc, Alexion, Altimmune, Antios Therapeuctics, AprosTx, Bayer, Cirina, Consumer Health Products Assoc, DiaSorin Inc, Dova Pharmaceuticals, DRG Abacus, Dynavax, Echosens, Eiger, Enyo, Exelixis, Forty-Seven Inc, Fujifilm Wako Diagnositics, Gilead, HepQuant, HepaTx, IDLogiq, Intellia, Intercept, Inotek, Iqvia, Janssen/J&J, KannaLife, Laboratory for Advanced Medicine, Labyrinth Holdings, Lilly, MedImmune, Merck, New Enterprise Associates, Ogilvy CommonHealth, Organovo, Patient Connect, ProdigY Biotech, Prometheus Laboratories, Refuah Solutions, Regulus Therapeutics, Salix, Shionogi, Spring Bank, Trimaran, and Viking Therapeutic, has speaker contracts with Abbvie, Bayer, Bristol Myers Squibb, Dova Pharmaceuticals, Eisai, Gilead, Intercept, Salix, and Shionogi, is a minor stock shareholder in RiboSciences, has stock options in Eiger, AngioCrine, and HepQuant;
- **M-FY** serves as advisor/consultant for AbbVie, Arbutus Biopharma, Bristol Myer Squibb, Dicerna Pharmaceuticals, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, Clear B Therapeutics and Springbank Pharmaceuticals, and receives grant/research support from Assembly Biosciences, Arrowhead Pharmaceuticals, Bristol Myer Squibb, Fujirebio Incorporation, Gilead Sciences, Merck Sharp and Dohme, Springbank Pharmaceuticals and Sysmex Corporation.
- **T-HL, WS, WC, DK-HW** and **KJ** have no disclosures

Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

JNJ-3989 and a nucleos(t)ide analogue: Mechanisms of action



- NAs inhibit viral replication but **do not prevent the production of HBsAg**
- Previously reported data up to **Day 112** (8 weeks after the JNJ-3989 dose) showed that treatment with JNJ-3989 (**100–400 mg**) in combination with an NA (TDF or ETV) resulted in **reductions in HBsAg, HBeAg, HBV RNA and HBcrAg**, and was well tolerated in patients with CHB[1]

1. Gane et al. APASL 2020. Oral presentation 777
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; NA = nucleos(t)ide analogue; pgRNA = pregenomic RNA; siRNA = short interfering RNA; TDF, tenofovir

Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

AROHBV1001: Study design

Open-label part in patients with CHB, focus on cohorts receiving JNJ-3989 3 X Q4w

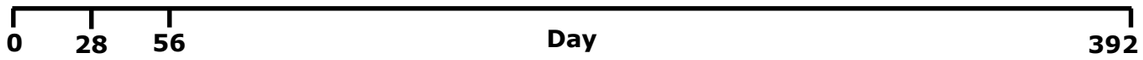
Study population:

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 beyond end of JNJ-3989 treatment

JNJ-3989 sc (100–400 mg) on Days 0, 28 and 56 plus a nucleos(t)ide analogue QD from Day 0 to Day 392



Assessments:

1. Viral parameters from Day 0 to Day 392, i.e, 48 weeks after the last JNJ-3989 dose
2. Safety from Day 0 to Day 336, i.e, 40 weeks after the last JNJ-3989 dose

JNJ-3989 3 x Q4w, cohort 2b–5b, 8 and 9

Cohort	N	JNJ-3989 dose
2b	8	100 mg
3b	8	200 mg
4b	8	300 mg
5b	8	400 mg
8 (HBeAg positive, NA-naïve)	4	300 mg
9 (HBeAg positive, NA-experienced)	4	300 mg

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

Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

AROHBV1001: Objectives of analysis

The objectives of this analysis of JNJ-3989 were to assess sustained response in **HBsAg**, **HBV RNA**, **HBeAg** and **HBcrAg** up to **Day 392**, 48 weeks after the last JNJ-3989 dose in patients with CHB continuing with NA treatment from Day 0 to end of study

Patients receiving 3 doses of JNJ-3989 (Q4w) 100–400 mg and having reached Day 392 were classified as sustained responders and non-sustained responders based on HBsAg response:

Sustained responder
≥1 $\log_{10}$ IU/mL reduction in HBsAg from Day 0 to Day 392

Non-sustained responder
<1 $\log_{10}$ IU/mL reduction in HBsAg from Day 0 to Day 392

Patients were included in the analyses if their HBsAg was reduced by ≥1 $\log_{10}$ IU/mL from Day 0 at any time through Day 392
CHB = chronic hepatitis B; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e-antigen;
HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IU, international units; NA = nucleos(t)ide analogue; Q4w = every 4 weeks

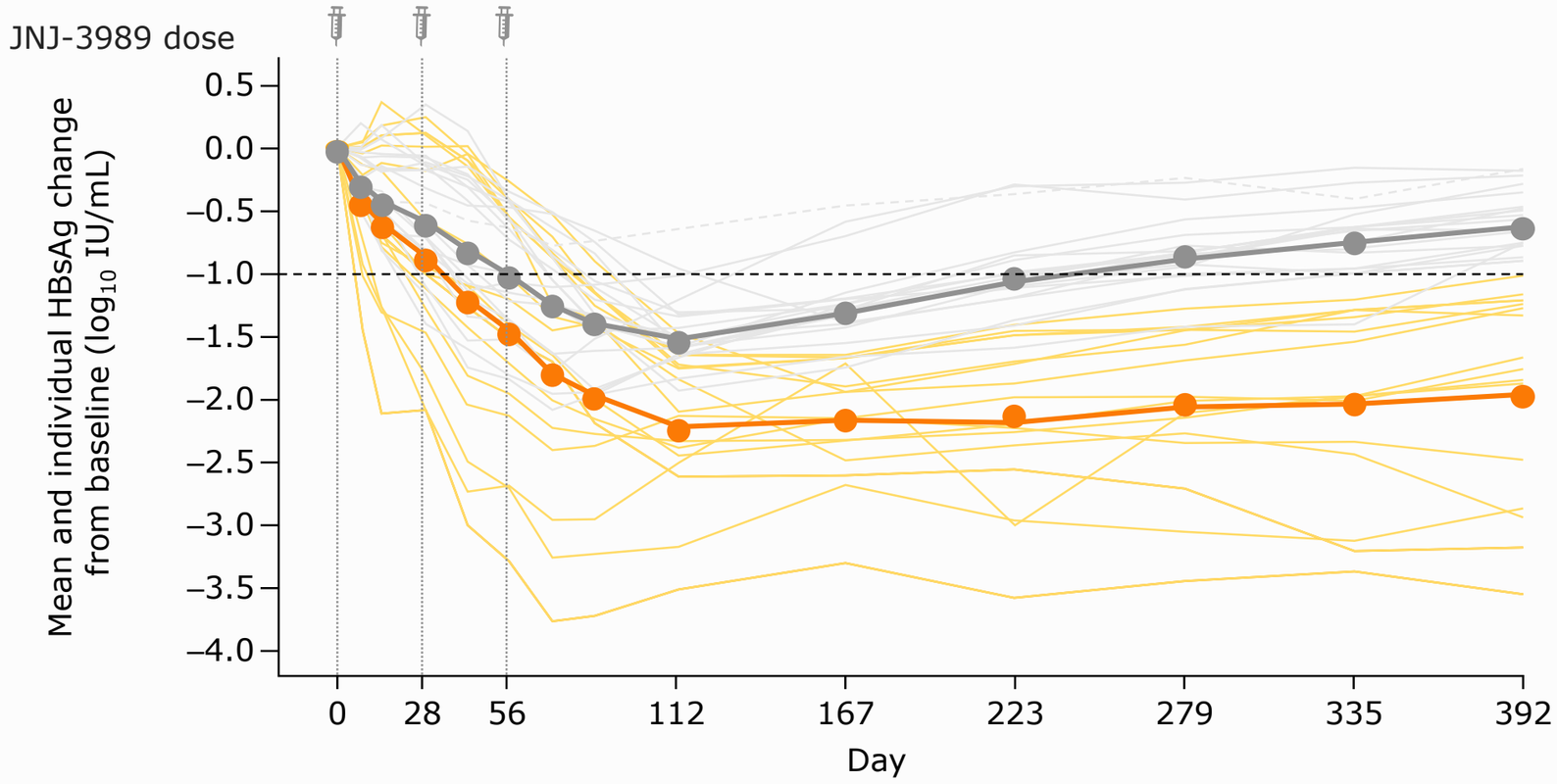
AROHBV1001: Baseline characteristics and demographics

	JNJ-3989 3 x Q4w, 100–400 mg cohort						
	Cohort 2b 100 mg N=8	**Cohort 3b 200 mg N=8**	**Cohort 4b 300 mg N=8**	**Cohort 5b 400 mg N=8**	**Cohort 8* 300 mg N=4**	**Cohort 9‡ 300 mg N=4**	**All patients N=40**
Age, years; mean (range)	51 (32.0–66.0)	48 (41.0–57.0)	52 (4.0–63.0)	42 (29.0–61.0)	37 (26.0–46.0)	36 (30.0–42.0)	45 (26.0–66.0)
Male, n (%)	6 (75.0)	5 (62.5)	8 (100.0)	6 (75.0)	2 (50.0)	2 (50.0)	29 (72.5)
Race, n (%) Asian Caucasian Other	 8 (100.0) 0 0	 8 (100.0) 0 0	 5 (62.5) 1 (12.5) 2 (25.0)	 6 (75.0) 0 2 (25.0)	 3 (75.0) 0 1 (25.0)	 4 (100.0) 0 0	 34 (85.0) 1 (2.5) 5 (12.5)
HBeAg positive (%)	1 (12.5)	1 (12.5)	3 (37.5)	1 (12.5)	4 (100.0)	4 (100.0)	14 (35.0)
NA experienced, n (%)	6 (75.0)	8 (100.0)	12 (75.0)	7 (87.5)	0	4 (100.0)	32 (80.0)
Mean (SEM) HBsAg on Day 1 (IU/mL)	3937 (2142.0)	3212 (2453.0)	9381 (8275.0)	4032 (1652.0)	137795 (8814.0)	7358 (2726.0)	18628 (10166.0)

*All patients in cohort 8 were HBeAg positive and NA-experienced at baseline. ‡All patients in cohort 9 were HBeAg positive and NA-naïve at baseline
HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; IU = international units; NA = nucleos(t)ide analogue;
Q4w = every 4 weeks; SEM = standard error of the mean

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

HBsAg sustained responders and non-responders



Off-treatment sustained HBsAg responders (**n=15**)

Off-treatment non-sustained HBsAg responders (**n=23**)

HBsAg non-responder (**n=1**)

In total, **15/38 (39%) patients** who were responders throughout the study were **sustained responders at Day 392**

Based on cohort 2b–5b, 8 and 9 data. Bold lines with circles represents mean values. Thin lines represent individual patients. Black dotted line represents change of -1 log_{10} IU/mL from Day 0 value.

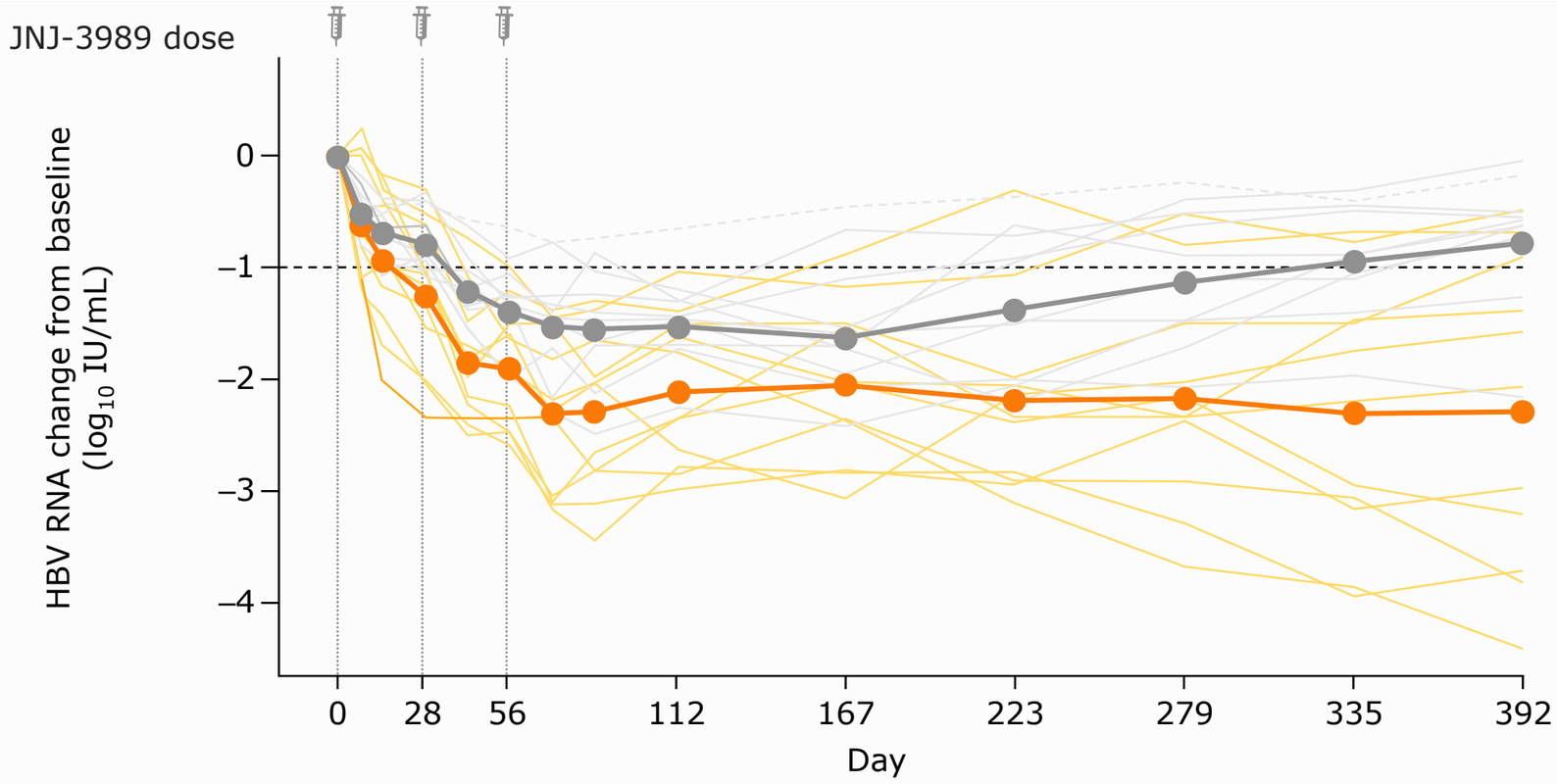
HBsAg = hepatitis B surface antigen; NA, nucleos(t)ide analogue; SE, standard error

Janssen Infectious Diseases & Vaccines

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

AROHBV1001: Effect of JNJ-3989 and NA treatment on HBV RNA levels

HBV RNA changes from baseline in HBsAg sustained responders and non-responders



Off-treatment sustained HBsAg responders (**n=11**)

Off-treatment non-sustained HBsAg responders (**n=9**)

HBsAg non-responder (**n=1**)

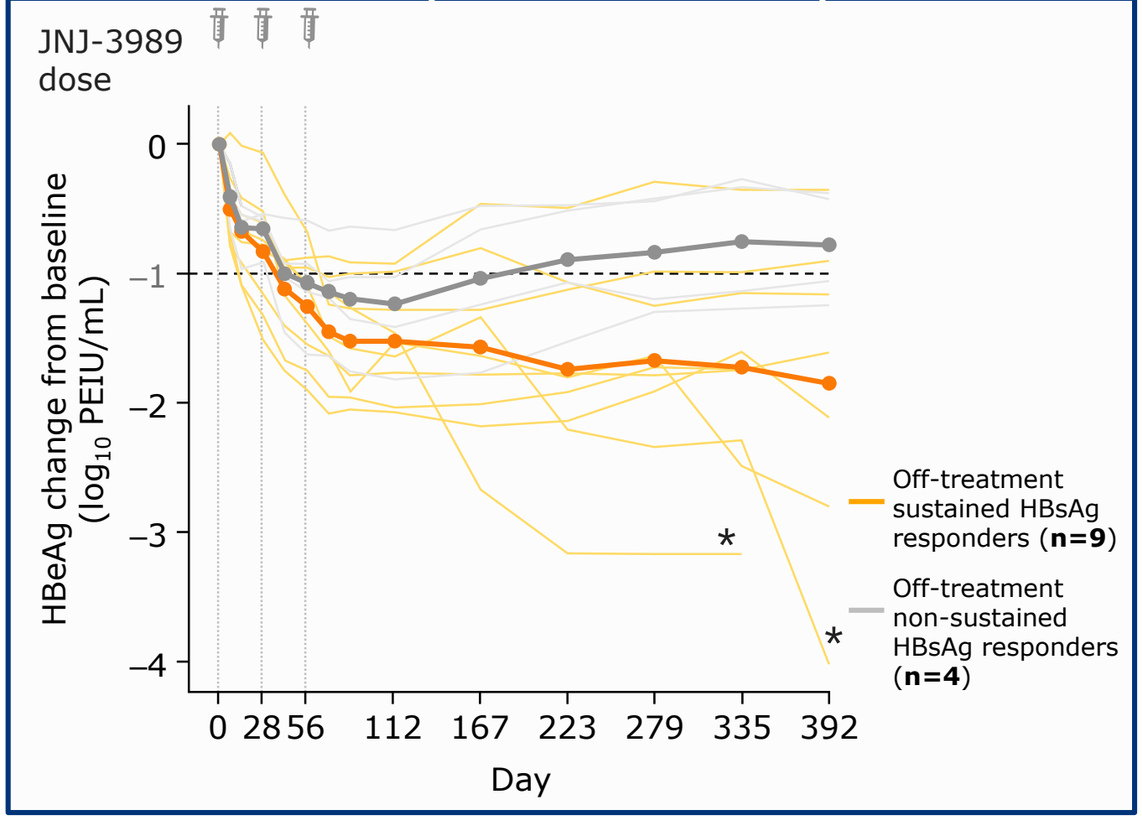
Reductions in HBV RNA levels were generally **more pronounced in HBsAg sustained responders** than non-responders through to Day 392

Based on cohort 2b–5b, 8 and 9 data. Only patients with HBV RNA levels >1log_{10} IU/mL above LLOQ were included in this analysis. Bold lines with circles represents mean values. Thin lines represent individual patients. Black dotted line represents change of −1 log^{10} IU/mL from Day 0.

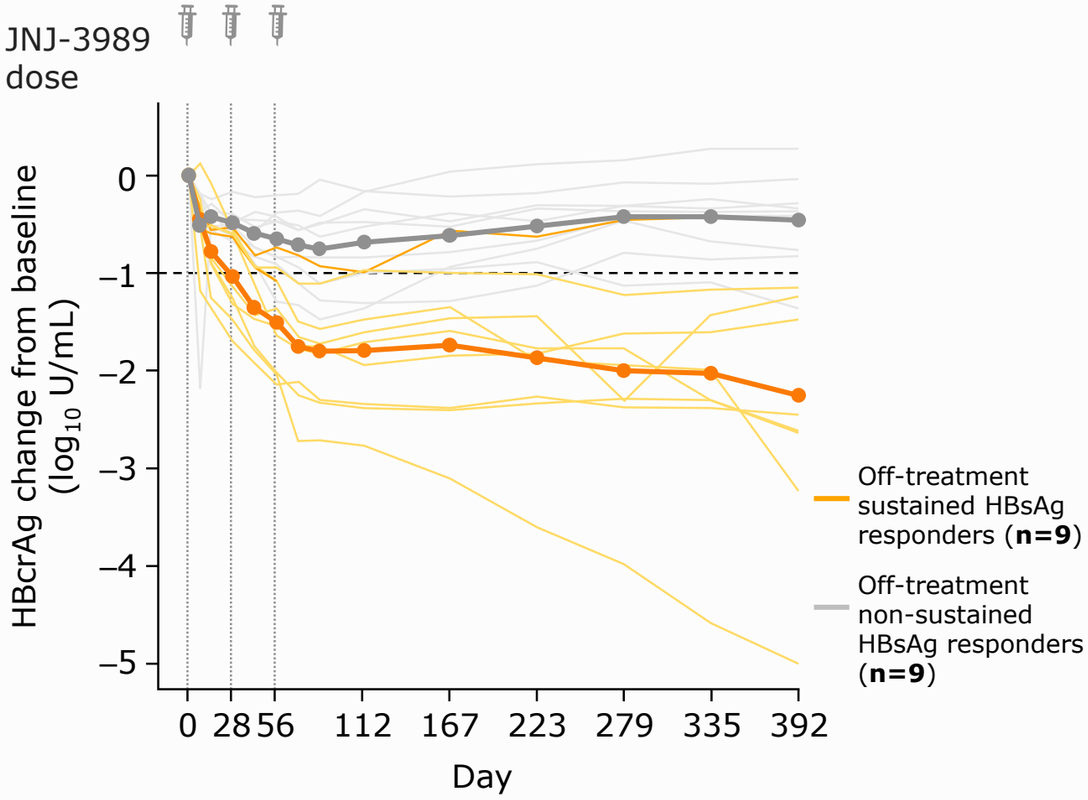
HBV = hepatitis B virus; IU = international units; NA = nucleos(t)ide analogue; SE, standard error

AROHBV1001: Effect of JNJ-3989 and NA treatment on HBeAg and HBcrAg

HBeAg changes from baseline in HBsAg sustained responders and non-responders



HBcrAg changes from baseline in HBsAg sustained responders and non-responders



Of the patients with quantifiable HBeAg and HBcrAg levels on Day 0, **greater reductions in HBeAg and HBcrAg** were seen in HBsAg sustained responders versus non-sustained responders

Based on cohort 2b–5b, 8 and 9 data. Only patients with HBeAg and HBcrAg levels >1log_{10} IU/mL above LLOQ were included in these analyses. Bold lines with circles represent mean values. Thin lines represent individual patients. Black dotted line represents change of −1 log_{10} IU/mL from Day 0.
*patients with HBeAg seroclearance events. HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e-antigen; NA = nucleos(t)ide analogue; PEIU = Paul Ehrlich international units; U, units; SE standard error

Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

AROHBV1001: Drug-related adverse events occurring through Day 336 after last JNJ-3989 dose

Drug-related AEs from Day 0 to Day 85							
Drug-related AEs in ≥ 2 patients, n (%)	**Cohort 2b N=8 100 mg**	**Cohort 3b N=8 200 mg**	**Cohort 4b N=8 300 mg**	**Cohort 5b N=8 400 mg**	**Cohort 8* N=4 300 mg**	**Cohort 9‡ N=4 300 mg**	**All arms N=40**
Injection site discoloration, injection site erythema, injection site bruising	0	0	2 mild (25.0)	2 mild (25.0)	2 mild (50.0)	1 mild (25.0)	7 (17.5)
Fatigue	1 mild (12.5)	0	0	1 mild (12.5)	0	0	2 (5.0)
Blood creatine kinase elevated	0	0	1 severe (12.5)	0	1 mild (25.0)	0	2 (5.0)
Blood bilirubin increased, hyperbilirubinemia	0	1 mild (12.5)	1 mild (12.5)	0	0	0	2 (5.0)
Muscle pain	0	0	1 mild (12.5)	1 mild (12.5)	0	0	2 (5.0)
Abdominal pain	0	1 mild (12.5)	0	1 mild (12.5)	0	0	2 (5.0)

There were no **new AEs drug-related reported** from Day 85 though Day 392, 48 weeks after the last JNJ-3989 dose

A single AE of possibly related abnormal liver function test **(peak ALT 136 U/L)** was reported

There were **no additional grade 3 or 4 laboratory abnormalities** during the treatment phase

Three non-drug related SAEs were reported: anxiety with depression in a single patient and menorrhagia, each requiring hospitalisation. All SAEs were resolved

*All patients in cohort 8 were HBeAg positive and NA-experienced at baseline. ‡All patients in cohort 9 were HBeAg positive and NA-naïve at baseline
AE = adverse event; SAE, serious adverse event

Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

AROHBV1001: Conclusions

For the first time in patients with CHB, siRNA therapy resulted in **sustained, off-treatment ≥1log$_{10}$ IU/mL reductions in HBsAg through to 48 weeks** after the last JNJ-3989 dose

- Reductions in **HBV RNA, HBeAg, HBcrAg** were **more pronounced in HBsAg sustained responders** than non-responders
- Three injections of JNJ-3989 (Q4w) were **well tolerated** at doses up to 400 mg and appeared to have a good long-term safety profile

- **These results support the evaluation of longer durations of treatment with JNJ-3989 + NA, with the objective of providing functional cure in patients with CHB**
  - 48-week phase 2b studies of JNJ-3989 + NA, with or without JNJ-6379 (CAM-N) are under way to assess functional cure rates in patients with CHB

CAM-N = capsid assembly modulator class N (inducing normal empty capsid formation) CHB = chronic hepatitis B; HBcrAg = hepatitis B core-related antigen; HBeAg = hepatitis B e-antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; NA = nucleos(t)ide analogue; Q4w = every 4 weeks

Janssen Infectious Diseases & Vaccines
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Acknowledgments

We express our gratitude to the patients who participated in this study. The authors also thank other Arrowhead staff members for their contributions to this study. This study was sponsored by Arrowhead Pharmaceuticals, Inc. Medical writing support for the development of this oral presentation was provided by Eleanor Coppins (Zoetic Science) Ashfield companies, part of UDG Healthcare plc, and was funded by Janssen Pharmaceuticals.