Treatment With siRNA JNJ-73763989 Plus Nucleos(t)ide Analogue (NA) Decreases HBsAg and HDV RNA Levels in Patients With Chronic Hepatitis D (CHD): Part 1 of the REEF-D Study

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REEF-D: Chronic Hepatitis D (CHD)

- Hepatitis D is the most severe form of chronic viral hepatitis
  - High risk for developing liver cirrhosis, decompensation, and HCC[1,2]
- PegIFN-α and bulevirtide (*conditional approval in the European Union*) can be used to treat hepatitis D[3]
- Limitations of current therapies:
  - PegIFN-α: low efficacy, side effects[4]
  - Bulevirtide: daily injections, long-term treatment, no effect on HBsAg levels[5]
- HDV requires HBsAg to form infectious viral particles[6]
- **Therefore, targeting HBsAg could be a therapeutic option for delta co-infection**

CHD, chronic hepatitis D; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; pegIFN, pegylated interferon.

1. Kamal H, et a. *Liver Int*. 2022. doi: 10.1111/liv.15467. 2. Alfaiate D, et al. *J Hepatol*. 2020;73(3):533-539. 3. EASL Clinical Practice Guidelines on hepatitis D. *J Hepatol.* 2023, epub June 24. 4. Sandmann L, Wedemeyer H. *Liver Int*. 2022 Aug 24. doi: 10.1111/liv.15410. 5. Lampertico P, Roulot D, Wedemeyer H. *J Hepatol*. 2022;77(5):1422-1430. 6. Urban S, Neumann-Haefelin C, Lampertico P. *Gut*. 2021;70(9):1782-1794.

REEF-D: siRNA JNJ-3989 in CHD

- JNJ-3989 is a liver-targeted siRNA that targets all HBV RNAs for degradation, thereby reducing all HBV proteins and pregenomic RNA[1]
- Results from phase 2a (NCT03365947, AROHBV1001)[2] and phase 2b (NCT03982186, REEF-1; NCT04129554, REEF-2)[3,4] clinical trials in patients with CHB have demonstrated pronounced reductions in HBsAg with JNJ-3989 (REEF-1: 48 weeks; 40, 100, and 200 mg; REEF-2: 48 weeks; 200 mg) in combination with NA
- In REEF-D, patients with CHD are treated with 100 mg JNJ-3989 Q4W SC + NA QD for up to 144 weeks
  - This is the first time an HBsAg targeting siRNA is used to treat patients with CHD
  - **Here, we report the 48-week interim analysis of Part 1 and available data after Week 48**

CHB, chronic hepatitis B; HBV, hepatitis B virus; JNJ-3989, JNJ-73763989; NA, nucleos(t)ide analogue; Q4W, every 4 weeks; QD, daily; SC, subcutaneous; siRNA, small interfering RNA.

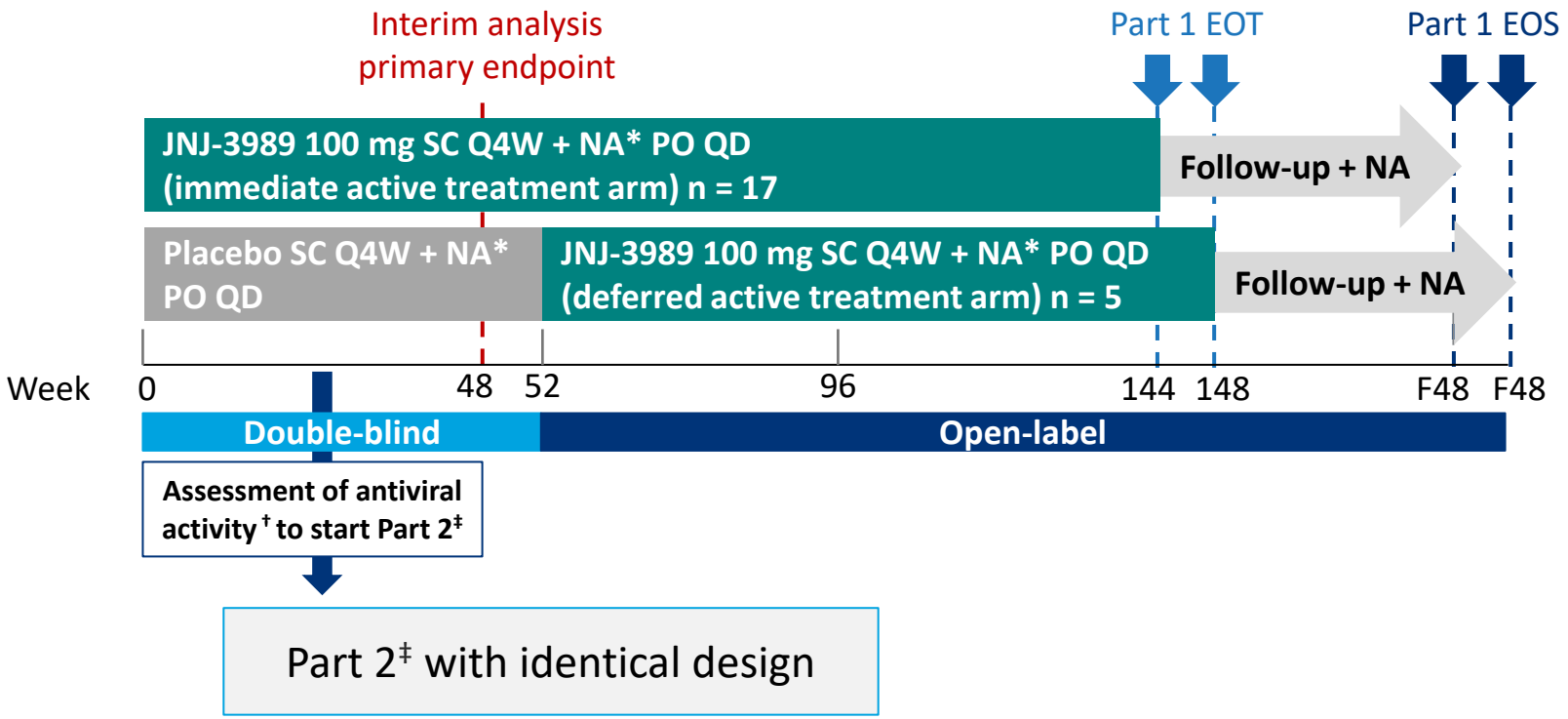
1. Gane E, et al. Presented at: European Association for the Study of the Liver (EASL) Digital International Liver Congress™; August 27-29, 2020; Virtual. Oral GS10.
2. Yuen MF, et al. *J Hepatol*. 2022;77(5):1287-1298. 3. Yuen MF, et al. *Lancet Gastroenterol Hepatol*. 2023. Accepted manuscript.
4. Agarwal K, et al. Presented at: American Association for the Study of Liver Diseases (AASLD) – The Liver Meeting®; November 4-8, 2022. Abstract 5012.

REEF-D (NCT04535544): Study Design

Phase 2, multicenter, randomized (4:1), 2-part, double-blind, placebo-controlled, parallel

- Patients aged 18 to 65 years
- Chronic hepatitis D: HDV RNA >1,000 IU/mL
- ALT >ULN and <10 × ULN
- Patients with compensated cirrhosis were eligible for Part 1 (platelets >100/nL)

Primary endpoint: HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or HDV RNA TND with normal ALT at Week 48



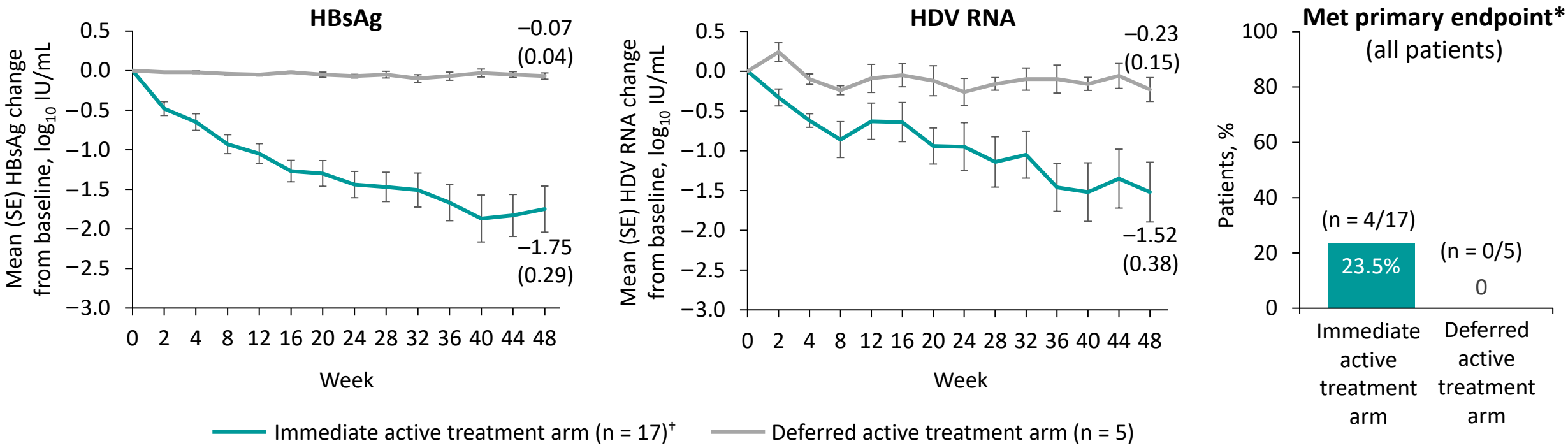
ALT, alanine transaminase; EOS, end of study; EOT, end of treatment; ETV, entecavir; F, follow-up; LLOQ, lower limit of quantification; PO, oral; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TND, <LLOQ target not detected.
*ETV/TDF/TAF according to label. †≥8 JNJ-3989–treated patients with ≥0.5 $\log_{10}$ reduction from baseline in HBsAg and HDV RNA and 4 of those with ≥1 $\log_{10}$ reduction in HDV RNA. ‡Part 2 of the study will be presented at a later date.

REEF-D: Demographic and Baseline Characteristics

Characteristic*	Immediate active treatment arm	Deferred active treatment arm	Total
N	17	5	22
Demographics			
Male, n (%)	9 (52.9)	2 (40.0)	11 (50.0)
Age, years	40.9 (10.4)	44.2 (11.9)	41.6 (10.6)
White, n (%)	13 (76.5)	4 (80.0)	17 (77.3)
Disease characteristics			
HBsAg, $\log_{10}$ IU/mL	4.1 (0.5)	3.8 (0.6)	4.0 (0.5)
HDV RNA, $\log_{10}$ IU/mL	5.1 (1.0)	5.1 (0.9)	5.1 (0.9)
HBV DNA <LLOQ, n (%)[†]	11 (64.7)	5 (100)	16 (72.7)
ALT, U/L	74.9 (48.0)	95.0 (87.2)	79.5 (57.2)
HBeAg positive, n (%)	3 (17.6)	1 (20.0)	4 (18.2)
NA treatment, n (%)[‡]	7 (41.2)	3 (60.0)	10 (45.5)
FibroScan® score, n (%)			
≥2 and <12.5 kPa	12 (70.6)	4 (80.0)	16 (72.7)
≥12.5 kPa	5 (29.4)	1 (20.0)	6 (27.3)

HBeAg, hepatitis B e antigen; SD, standard deviation.
*Mean (SD) unless otherwise noted. [†]HBV DNA <LLOQ (20 IU/mL). [‡]Patients on NA treatment at screening.

REEF-D: Change in HBsAg and HDV RNA Over Time



- Treatment with JNJ-3989 led to robust reductions in HBsAg and HDV RNA
- The antiviral activity criteria‡ to start Part 2 of the study were met

SE, standard error.
*HDV RNA ≥2 log_{10} IU/mL decline from baseline or undetectable in combination with normal ALT at Week 48. †Data in the immediate active arm are available for 17 patients up to Week 12, and for 14, 11, and 9 patients at Weeks 24, 36, and 48, respectively, due to early JNJ-3989 treatment discontinuation. ‡8 JNJ-3989–treated patients with ≥0.5 log_{10} reduction from baseline in HBsAg and HDV RNA, and 4 of those with ≥1 log_{10} reduction in HDV RNA.

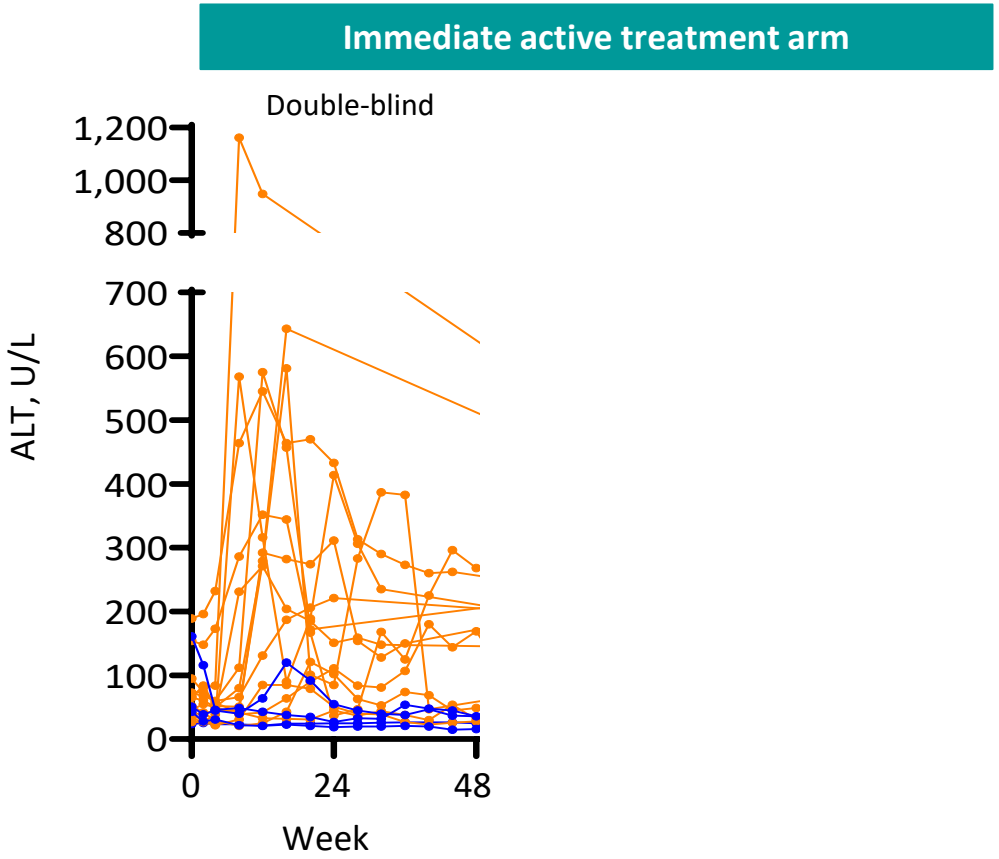
REEF-D: Safety

	Immediate active treatment arm (n = 17)	Deferred active treatment arm (n = 5)
Patients with ≥1 AEs, n (%)	17 (100)	3 (60.0)
Related AEs	12 (70.6)	1 (20.0)
Related to JNJ-3989/placebo	11 (64.7)	1 (20.0)
Related to NA	4 (23.5)	1 (20.0)
AEs leading to death	0	0
SAEs, n (%)	2 (11.8)	0
Related SAEs*	2 (11.8)	0
AEs leading to discontinuation of any study treatment, n (%)†	4 (23.5)	0
Grade 3 or 4 AEs, n (%)‡	6 (35.3)	0
Related Grade 3 or 4 AEs	6 (35.3)	0
AEs of special interest, n (%)		
ALT§/AST elevations	13 (76.5)	0
Injection-site reactions	1 (5.9)	0
Renal complications	0	0
Cholesterol increases	2 (11.8)	0
Hematologic abnormalities	0	0

- Of 6 patients with **compensated cirrhosis**, 5 received JNJ-3989 and 4 experienced an ALT elevation; safety profiles were not different from non-cirrhotic patients, with **no signs of reduced liver function during flare**

AE, adverse event; AST, aspartate transaminase; SAE, serious adverse event.
*Transaminases increased and ALT/AST flare occurred in 1 patient each. †Not all ALT/AST elevations leading to discontinuation prior to Week 48 (n = 8) were reported as AEs.
‡No cases of decompensation. §Confirmed (2 consecutive visits) ALT ≥3 × ULN and ≥2 × nadir

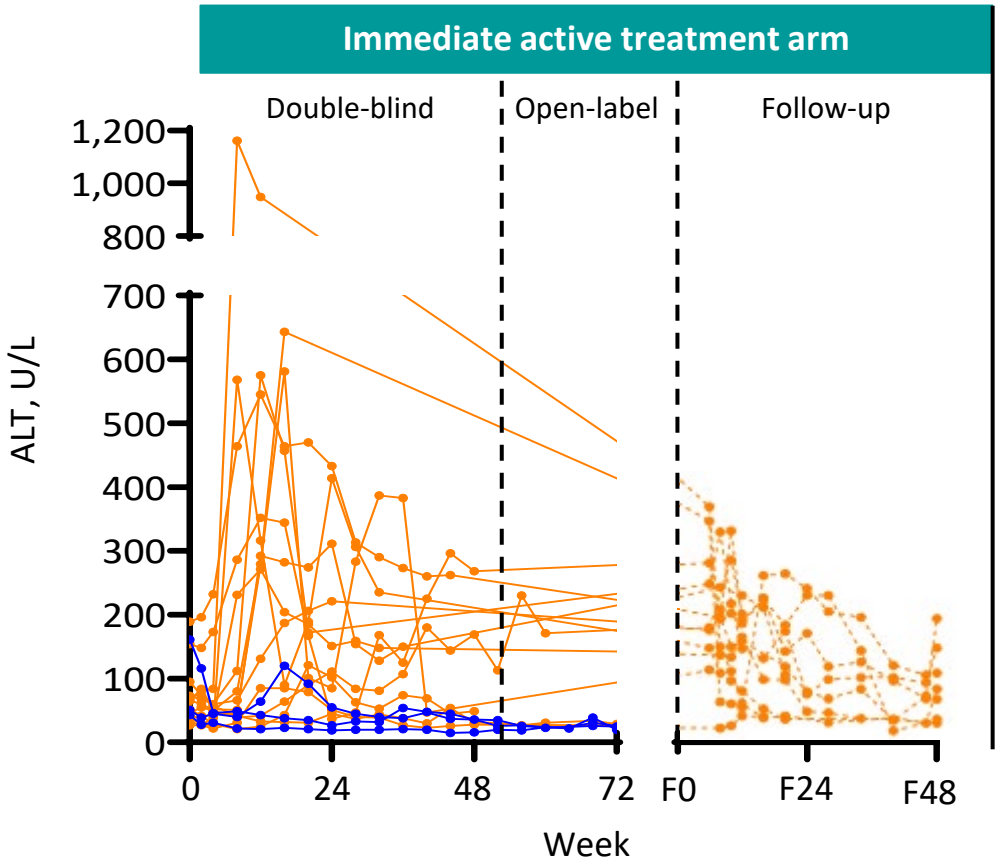
REEF-D: Individual ALT Levels Over Time by Baseline HBsAg Level



- 12/17 patients in the immediate active treatment arm experienced ALT elevations† (starting mainly between weeks 8 and 20)

*Confirmed (2 consecutive visits) ALT ≥3 × ULN and ≥2 × nadir.

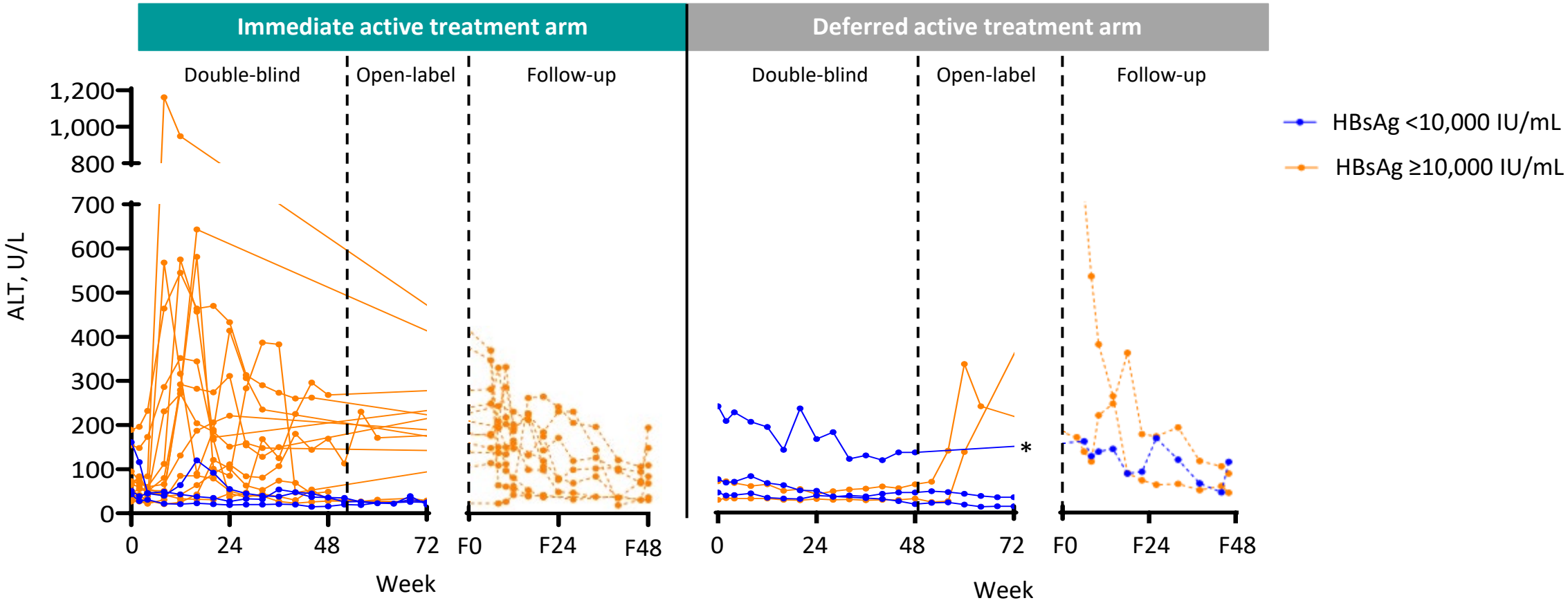
REEF-D: Individual ALT Levels Over Time by Baseline HBsAg Level



- 12/17 patients in the immediate active treatment arm experienced ALT elevations† (starting mainly between weeks 8 and 20) leading to treatment discontinuation

Available data beyond Week 48 are included. F, follow-up.
*Confirmed (2 consecutive visits) ALT ≥3 × ULN and ≥2 × nadir.

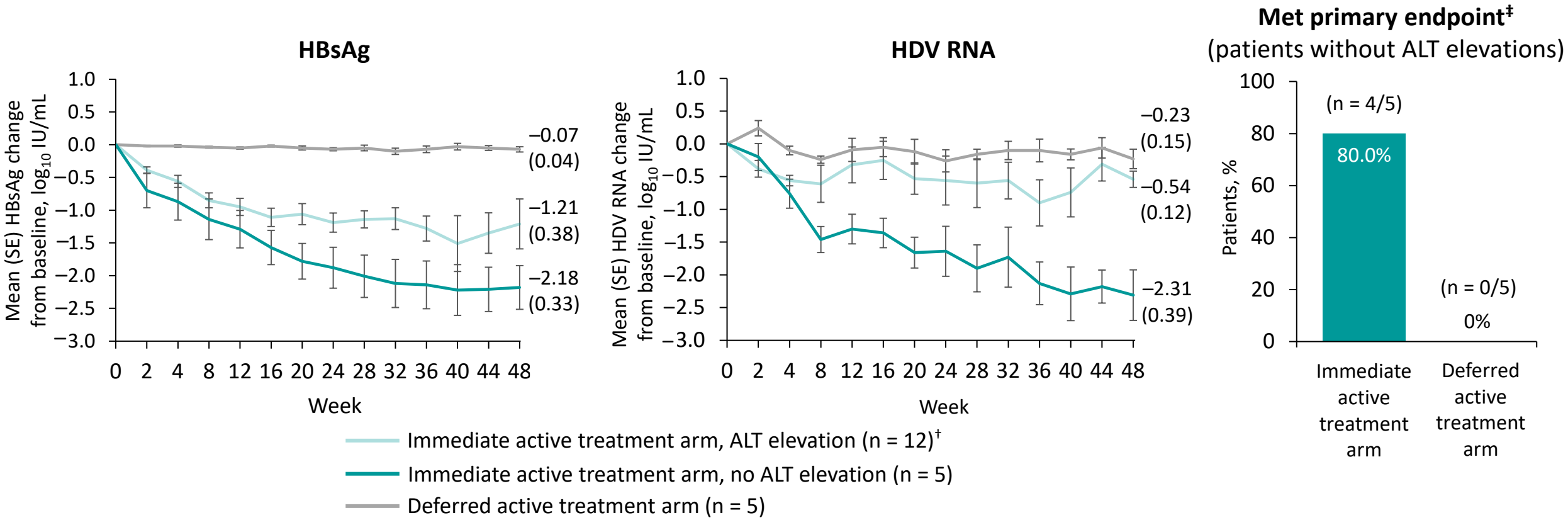
REEF-D: Individual ALT Levels Over Time by Baseline HBsAg Level



- 12/17 patients in the immediate active treatment arm experienced ALT elevations† (starting mainly between weeks 8 and 20) leading to treatment discontinuation

Available data beyond Week 48 are included. F, follow-up.
†Confirmed (2 consecutive visits) ALT ≥3 × ULN and ≥2 × nadir.
*This patient did not receive JNJ-3989 during the open-label phase and moved directly to the follow-up phase due to cirrhosis.

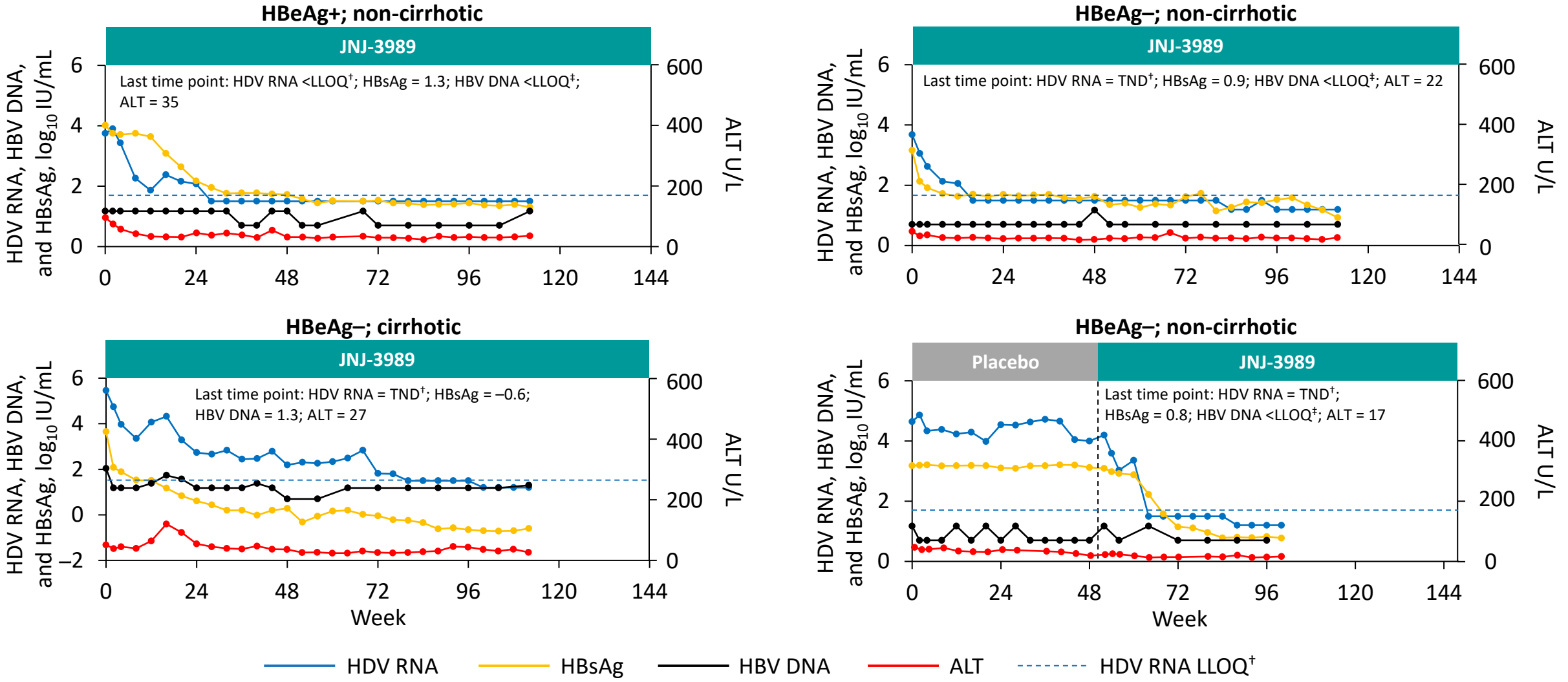
REEF-D: HBsAg and HDV RNA Over Time by ALT Elevation* Status



- ALT elevations* were associated with on-treatment rebound of HDV RNA

*Confirmed (2 consecutive visits) ALT ≥3 × ULN and ≥2 × nadir. †Data in this group are available for 12, 9, 6, and 4 patients at Weeks 12, 24, 36, and 48, respectively.
‡HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline or undetectable in combination with normal ALT at Week 48.

REEF-D: Representative Patient Profiles Without ALT Elevations*

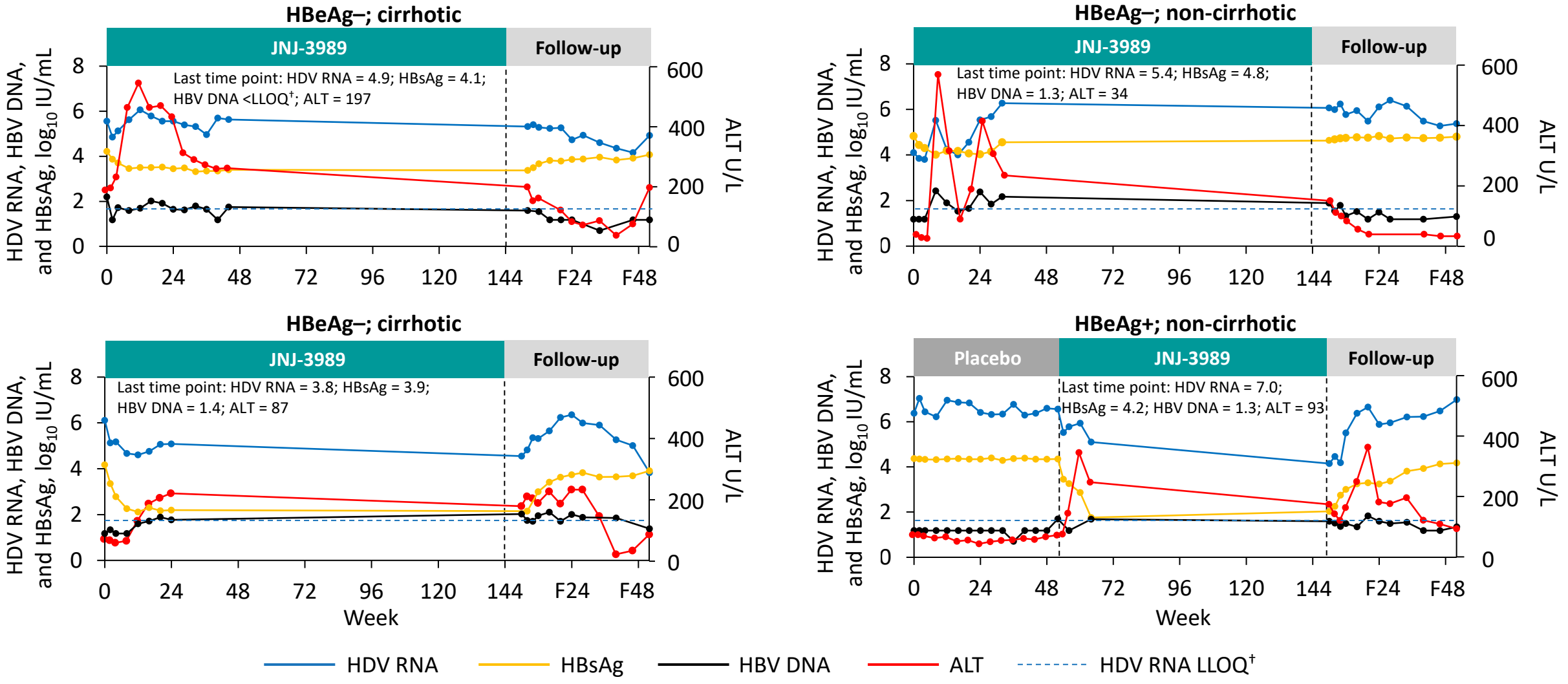


All available data beyond Week 48 are shown.

*Confirmed (2 consecutive visits) ALT ≥3 × ULN and ≥2 × nadir. †HDV RNA LLOQ = 1.8 $\log_{10}$ IU/mL. TND: <LLOQ target not detected.

‡HBV DNA <LLOQ = 1.3 $\log_{10}$ IU/mL

REEF-D: Representative Patient Profiles With ALT Elevations*



All available data beyond Week 48 are shown.
NCT, not currently treated.
*Confirmed (2 consecutive visits) ALT ≥3 × ULN and ≥2 × nadir. †HBV DNA <LLOQ = 1.3 $\log_{10}$ IU/mL.

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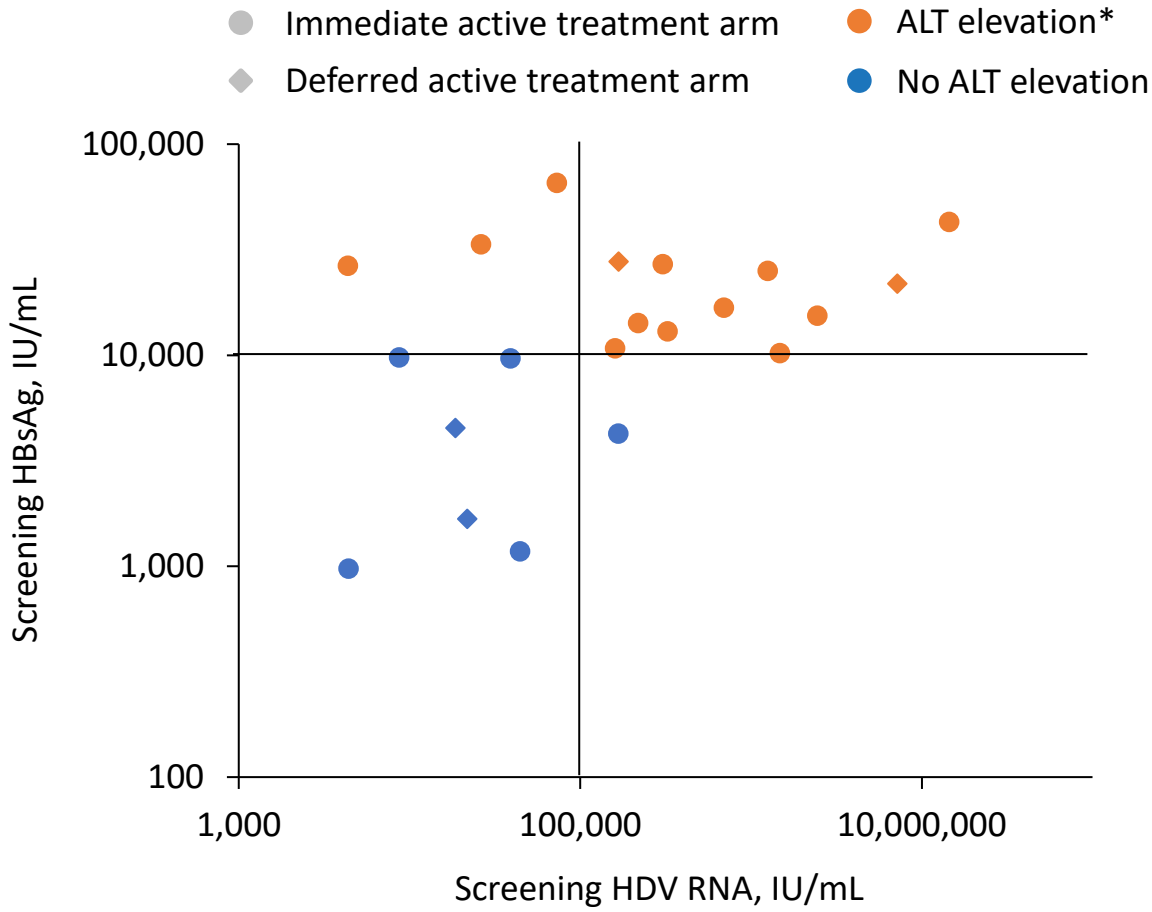
REEF-D: Screening Factors Associated With ALT Elevations*

Number of patients	ALT elevation*	No ALT elevation
HDV RNA <100,000 IU/mL	3	6
HDV RNA ≥100,000 IU/mL	11	1
HBsAg <10,000 IU/mL	0	7
HBsAg ≥10,000 IU/mL	14	0
Compensated cirrhosis, yes	4	1
Compensated cirrhosis, no	10	6
NA: TDF/TAF	12	6
NA: ETV	2	1



- ALT elevations* were more frequent in patients with high screening HBsAg and HDV RNA levels

21 patients receiving JNJ-3989 were included in this analysis (1 deferred active treatment arm patient with cirrhosis was excluded due to not receiving JNJ-3989).
*Confirmed (2 consecutive visits) ALT ≥3 × ULN and ≥2 × nadir.

REEF-D: Summary

- JNJ-3989 led to robust reductions of HBsAg and HDV RNA (observed in all patients up until Week 8)
- 12/17 (71%) patients in the immediate active treatment arm and 2/4 (50%) patients in the deferred active treatment arm (after rollover to JNJ-3989 at Week 52) experienced ALT elevations* that eventually led to discontinuation of JNJ-3989
  - During ALT elevations* HDV RNA levels rebounded
  - During follow-up, ALT values returned to baseline levels
- 5/17 (29%) patients in the immediate active treatment arm and 2/4 (50%) patients in the deferred active treatment arm did not experience ALT elevations*
  - At Week 48 of JNJ-3989 treatment, 5/7 (71%) patients achieved HDV RNA ≥2 $\log_{10}$ IU/mL decline from baseline with normal ALT
  - At the last available time point, all 7 patients showed continuous reductions of HBsAg and HDV RNA and 4 patients achieved HDV RNA <LLOQ (3 patients TND) with JNJ-3989 treatment lasting up to 112 weeks

*Confirmed (2 consecutive visits) ALT ≥3 × ULN and ≥2 × nadir.

REEF-D: Conclusions

- The HBsAg-targeting agent JNJ-3989 leads to reduction of HBsAg and HDV RNA early during treatment in patients with CHD
- The antiviral activity criteria to start Part 2 of the study were met, and treatment in Part 2, with adapted inclusion criteria, is ongoing
- Clinically relevant ALT elevations* are frequently observed, during which, HDV RNA rebounded
  - The underlying mechanism is not understood
  - A similar pattern of ALT elevation* was not seen in HBV mono-infected patients treated with JNJ-3989
  - The risk of ALT elevation* was greater in patients with high HBsAg (≥10,000 IU/mL) and HDV RNA (≥100,000 IU/mL) levels at baseline
- In the absence of ALT elevation,* pronounced reductions in HDV RNA are maintained with continued treatment

*Confirmed (2 consecutive visits) ALT ≥3 × ULN and ≥2 × nadir.

Acknowledgments

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