Why may siRNAs induce Flares in HBV/HDV Co-Infection?

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GHE | Gastroenterologie Hepatologie Infektiologie Endokrinologie

MHH

Medizinische Hochschule Hannover

Conflicts of Interest

Honoraria for consulting or speaking (last 5 years):

Abbott, AbbVie, Abivax, Bayer, Biotest, BMS, BTG, Eiger, Enanta, Esei, Falk Foundation, Gilead, JJ/Janssen-Cilag, MSD, MyrGmbH, Norgine, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, Vaccitec, Vir

Research grants:

Abbott, Abbvie, Biotest, BMS, Gilead, Merck, Novartis, Roche, Roche Diagnostics

The cascade of care for patients with chronic hepatitis delta in Southern Stockholm, Sweden for the past 30 years.

Kamal H, Lindahl K, Ingre M, Gahrton C, Karkkonen K, Nowak P, Vesterbacka J, Stål P, Wedemeyer H, Duberg AS, Aleman S.
Liver Int. 2023 Oct 30. doi: 10.1111/liv.15770. Online ahead of print.

Clinical long-term outcome of hepatitis D compared to hepatitis B monoinfection.

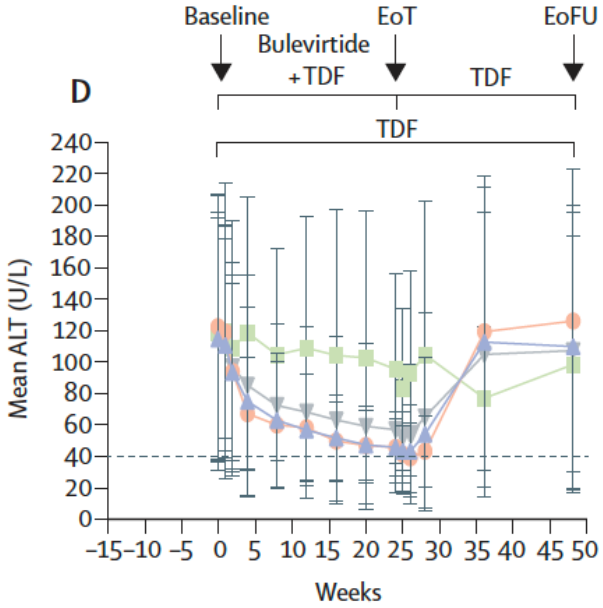
Wranke A, Heidrich B, Deterding K, Hupa-Breier KL, Kirschner J, Bremer B, Cornberg M, Wedemeyer H.
Hepatol Int. 2023 Oct 3. doi: 10.1007/s12072-023-10575-0. Online ahead of print.

Five-year follow-up of 96 weeks peginterferon plus tenofovir disoproxil fumarate in hepatitis D.

Anastasiou OE, Caruntu FA, Curescu MG, Yalcin K, Akarca US, Gürel S, Zeuzem S, Erhardt A, Lüth S, Papatheodoridis GV, Keskin O, Port K, Radu M, Celen MK, Idilman R, Heidrich B, Mederacke I, von der Leyen H, Kahlhöfer J, von Karpowitz M, Hardtke S, Cornberg M, Yurdaydin C, Wedemeyer H.
Liver Int. 2023 Oct 3. doi: 10.1111/liv.15745. Online ahead of print.c

ALT and Viral Load in Hepatitis D

- Decline of HDV RNA is associated with improvements in ALT levels



Wedemeyer et al. Lancet Infect Dis 2023 Jan;23(1):117-129

ALT and Viral Load in Hepatitis D

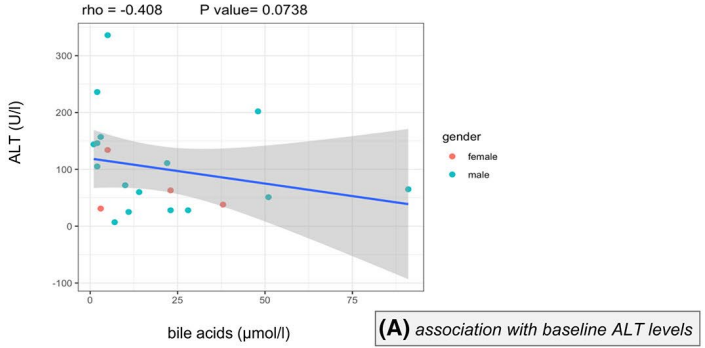
- Decline of HDV RNA is associated with improvements in ALT levels

Relationship Between ALT Normalization Rates and Different Virologic Response Criteria in Chronic HDV Patients Treated With Bulevirtide Monotherapy

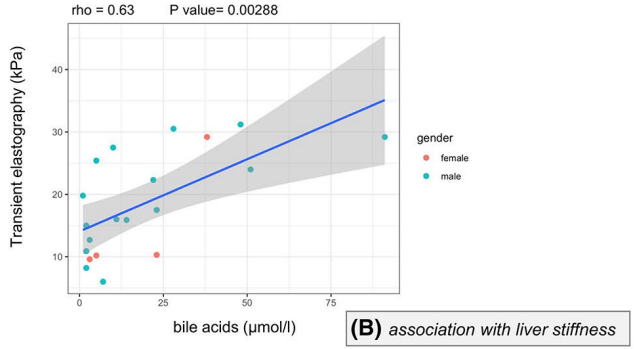
Pietro Lampertico[1,2], Soo Aleman[3], Pavel Bogomolov[4], Tatyana Stepanova[5], Markus Cornberg[6], Sandra Ciesek[7], Annemarie Berger[7], Dmitry Manuilov[8], Qi An[8], Audrey H Lau[8], Ben L Da[8], John F Flaherty[8], Renee-Claude Mercier[8], Yang Liu[8], Maurizia Rossana Brunetto[9], Stefan Zeuzem[10], Heiner Wedemeyer[6]

Lampertico et al. Poster AASLD- The Liver Meeting 2023

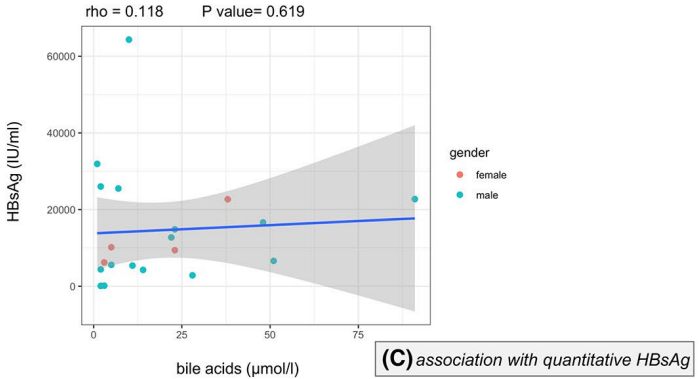
ALT and Bile Acids in Hepatitis D



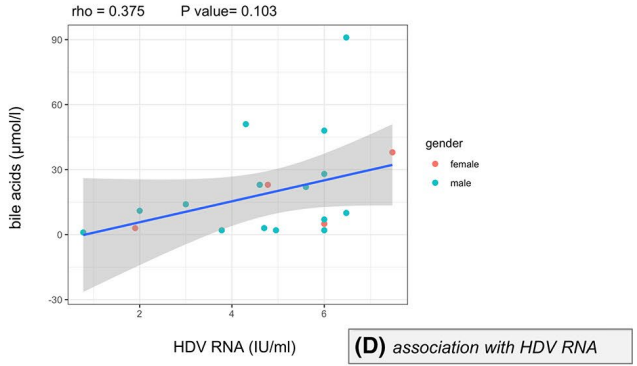
(A) *association with baseline ALT levels*



(B) *association with liver stiffness*



(C) *association with quantitative HBsAg*



(D) *association with HDV RNA*

Deterding et al., J Viral Hepatitis 2023

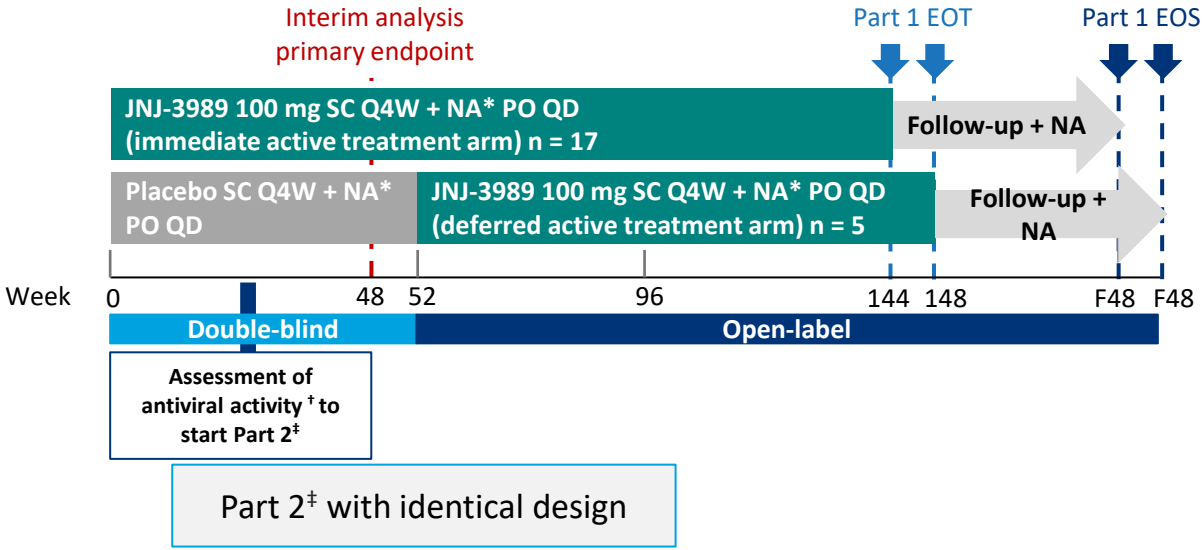
REEF-D

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

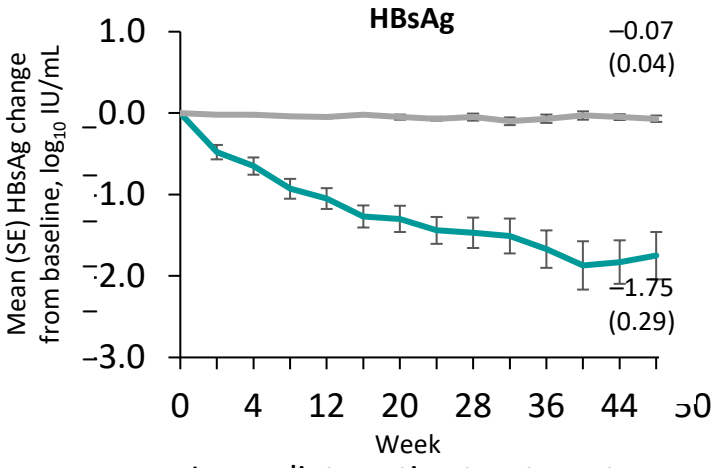


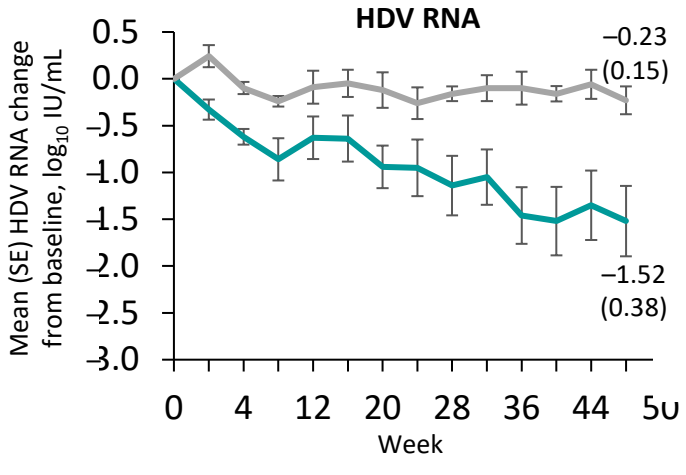
ALT, alanine transaminase; EOS, end of study; EOT, end of treatment; ETV, entecavir; F, follow-up; LLOQ, lower limit of quantification; PO, oral; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TND, <LLOQ target not detected.

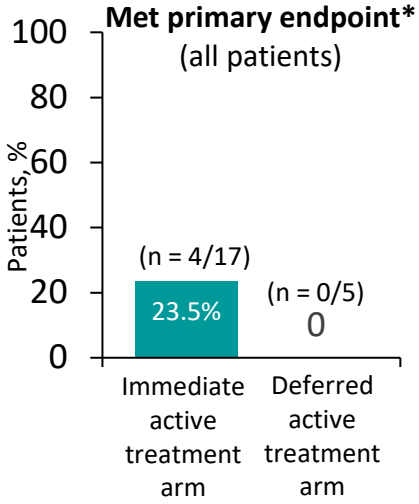
*ETV/TDF/TAF according to label. †≥8 JNJ-3989–treated patients with ≥0.5 $\log_{10}$ reduction from baseline in HBsAg and HDV RNA and 4 of those with ≥1 $\log_{10}$ reduction in HDV RNA. ‡Part 2 of the study will be presented at a later date.

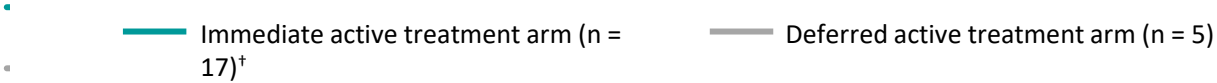
Wedemeyer H, et al. EASL 2023

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.

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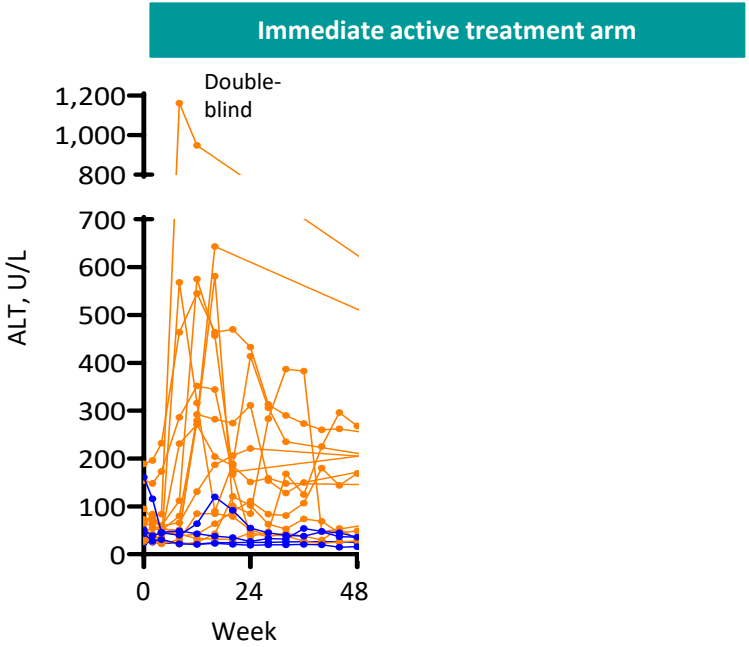
REEF-D: Individual ALT Levels Over Time by Baseline HBsAg Level



- 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.

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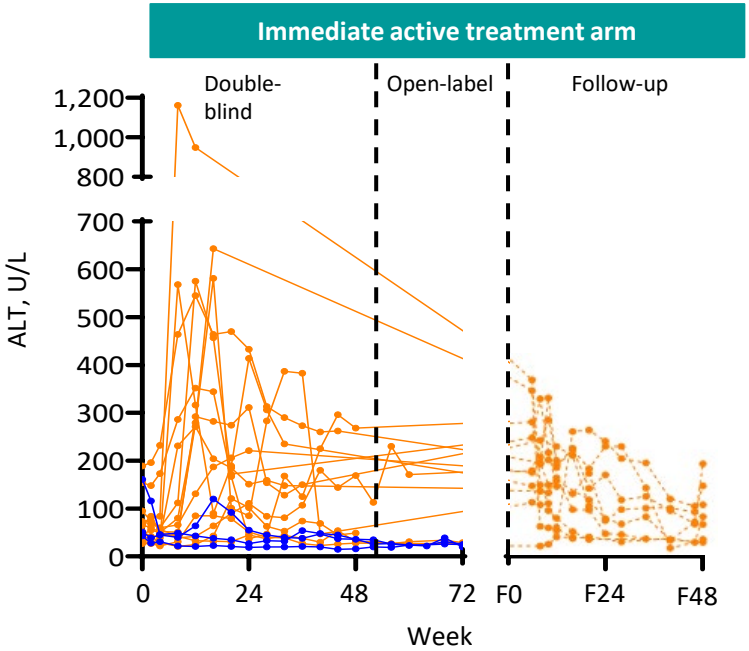
REEF-D: Individual ALT Levels Over Time by Baseline HBsAg Level



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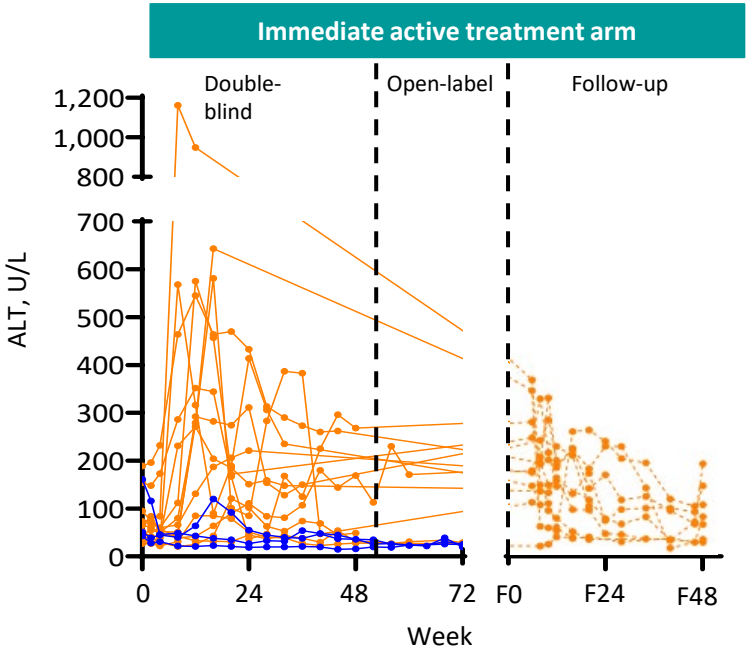
REEF-D: Individual ALT Levels Over Time by Baseline HBsAg Level



HBsAg <10,000 IU/mL

HBsAg ≥10,000 IU/mL

- 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.

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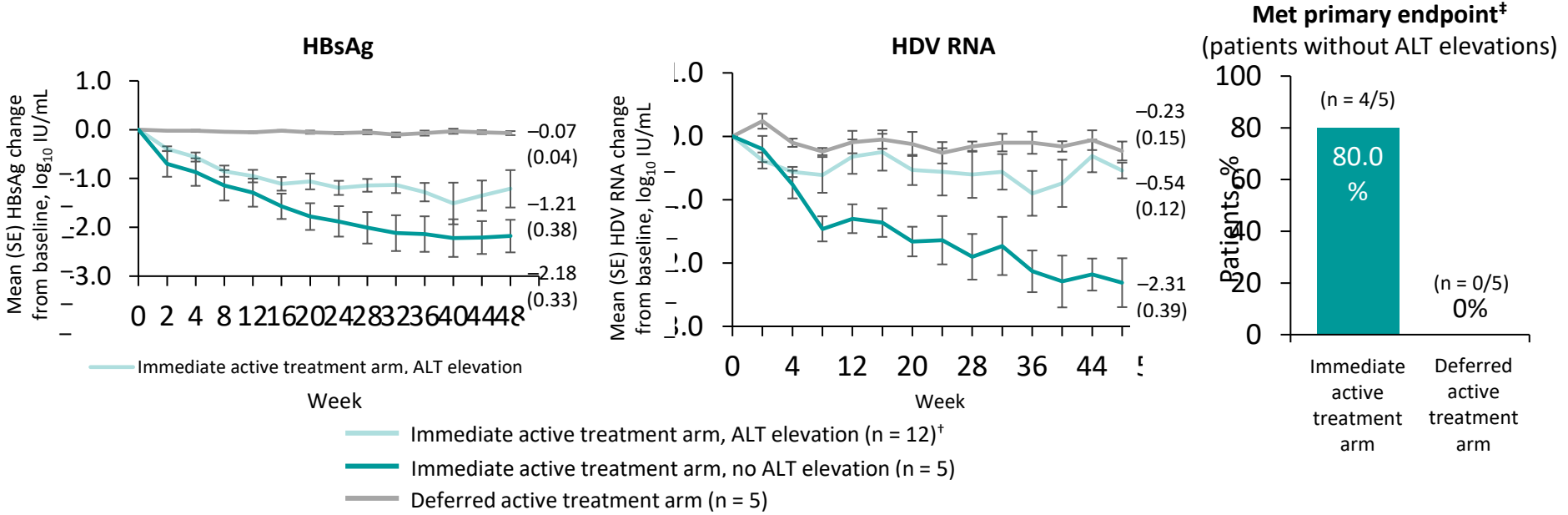
REEF-D: HBsAg and HDV RNA Over Time by ALT Elevation* Status



- 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.

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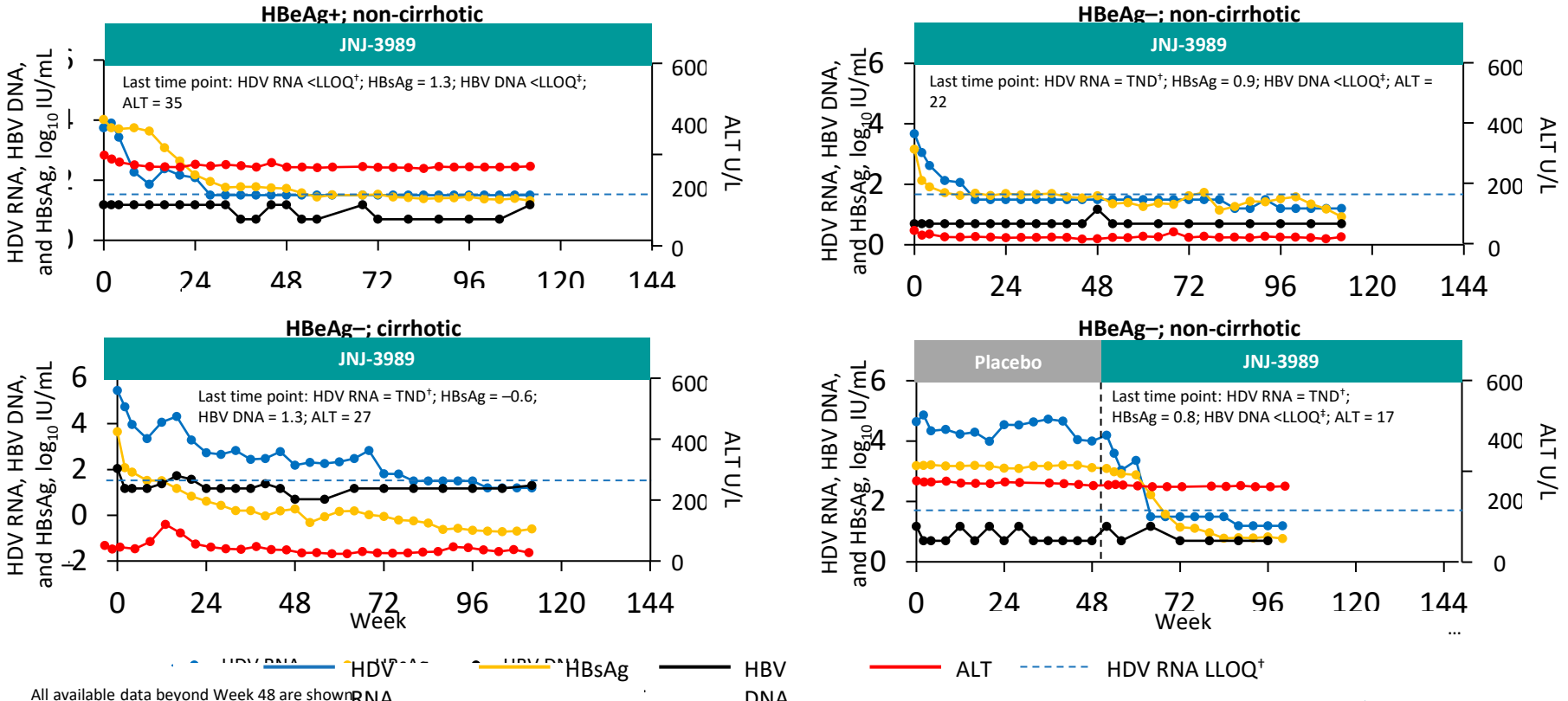
REEF-D: Representative Patient Profiles Without ALT Elevations*



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

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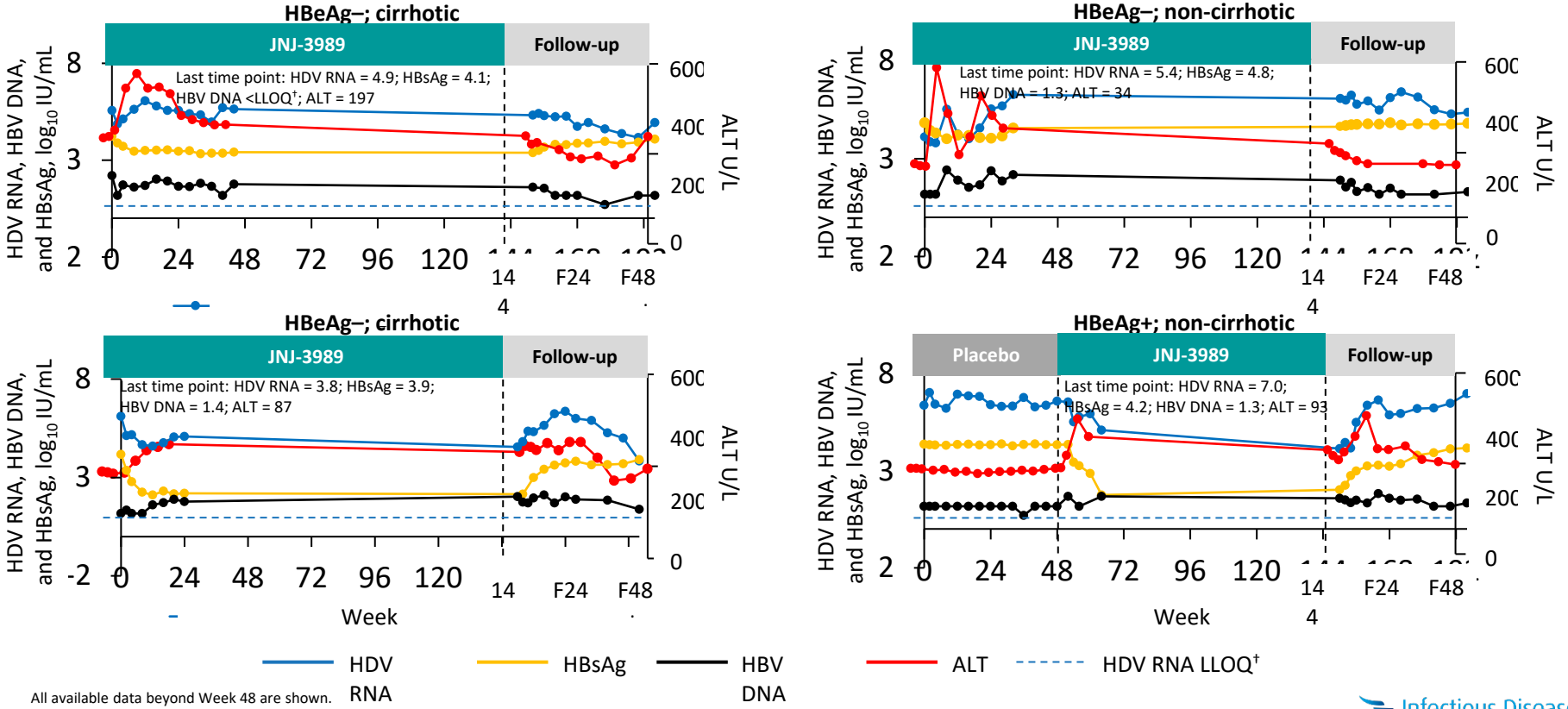
REEF-D: Representative Patient Profiles With ALT Elevations*



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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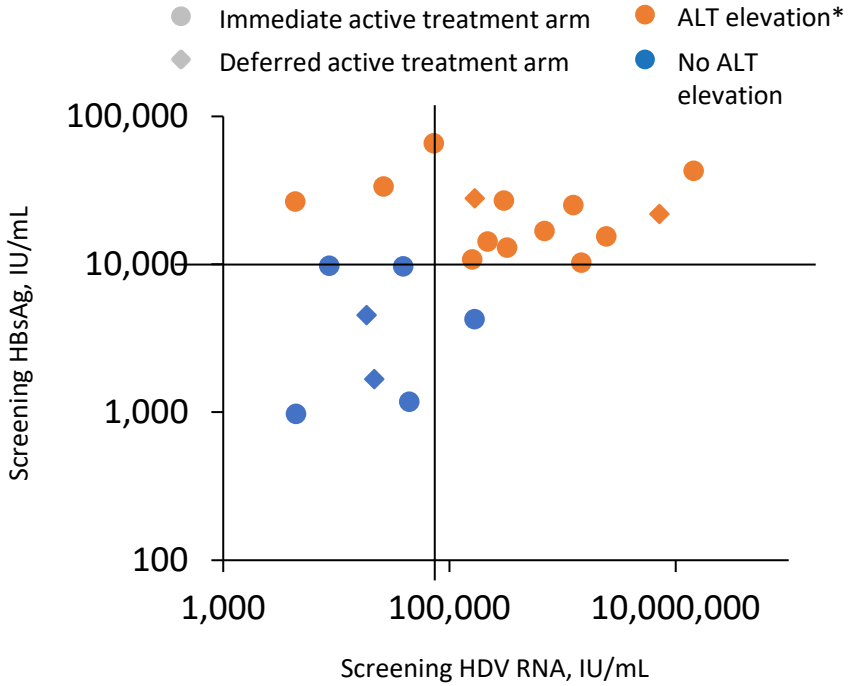
REEF-D: Screening Factors Associated With ALT Elevations*

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.
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Preliminary learnings about ALT elevations in HDV

- Clinically relevant ALT elevations* were observed in HBV/HDV patients treated with HBsAg targeting siRNA JNJ-3989
  - A pattern of ALT elevations not seen in HBV mono-infected patients (>500 patients treated with JNJ-3989)
  - ALT elevations were associated with increases in HDV RNA and limited HBV DNA elevation (under NA treatment). No apparent impact on JNJ-3989 induced HBsAg decline.
  - ALT elevations were more frequent in patients with high screening HBsAg and HDV RNA levels.

- In patients with ALT elevations:
  - Upregulation of anti-inflammatory cytokines IL-10 and TNF and immunosuppressive markers CD73 and TRIM23. Different from upregulation of IL-7, CXCL5 and DNER described during ALT elevation in PegIFN treated HBV/HDV patients?
  - Strong association between ALT elevations and increased apoptosis markers (KRT18, C19orf12).

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

1 Anastasiou et al 2020

siRNAs against HBV in HDV

- Will we see flares when anti-HBs-siRNAs are combined with other anti-HBV drugs (bulevirtide, antibodies, etc.)?

"The monoclonal antibody VIR-3434 and siRNA VIR-2218 for the treatment of chronic hepatitis D virus: preliminary results from the phase 2 SOLSTICE trial"

Session Title: *Late Breaking Abstract #1*
Presentation Type: Oral, Late Breaking Parallel Session
Session Date and Time: Monday, November 13, 2023, 2:00 PM - 3:30 PM
Presentation Time: 3:00 PM

siRNAs against HBV in HDV

- Will we see flares when anti-HBs-siRNAs are combined with other anti-HBV drugs (bulevirtide, antibodies, etc.)?
- Mechanisms explaining flares in individual patients?
- **Long-term use (in selected patients) could be an opportunity!**