Durable and newly emergent treatment response during a 24-week follow-up in a finite lonafarnib treatment regimen:

extended analyses from the phase 3 D-LIVR trial

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The results presented here describe findings from clinical studies of an investigational product that has not been approved by the U.S. Food and Drug Administration or any other regulatory agency. All data should be interpreted as preliminary and subject to confirmation in ongoing or future clinical trials.

EIT PHARMA

HDV: a serious disease with unmet medical need

Hepatitis delta virus (HDV) is the most severe viral hepatitis

HBV patients who are HDV+ have a 2.2-fold higher risk of liver-related complications[1]

HDV represents a serious unmet medical need

HDV prevalence is likely underestimated as routine HDV screening is not widely implemented even among HBV patients[2].
There continues to be critical need for novel, accessible therapeutics that target distinct steps in the HDV cycle.

The treatment landscape for HDV remains limited

A single therapeutic (chronic bulevirtide injection) has been approved in the US and EU
Lonafarnib remains the only HDV treatment option in advanced development with[3]:

- **Oral route of administration**
- **Fixed treatment course**

1: *Asselah T,* Rizzetto M. Hepatitis D Virus Infection. *N Engl J Med.* 2023; 389(1):58-70.
2. Wong, R. et al. *Liver International.* 2024: 44(7): 1715-1734.
3. Haddadin et al. *Antiviral Research*. 2026: 252,

Lonafarnib inhibits a key step in viral assembly

Lonafarnib's unique MOA targets assembly of viral particles preventing formation of infective HDV

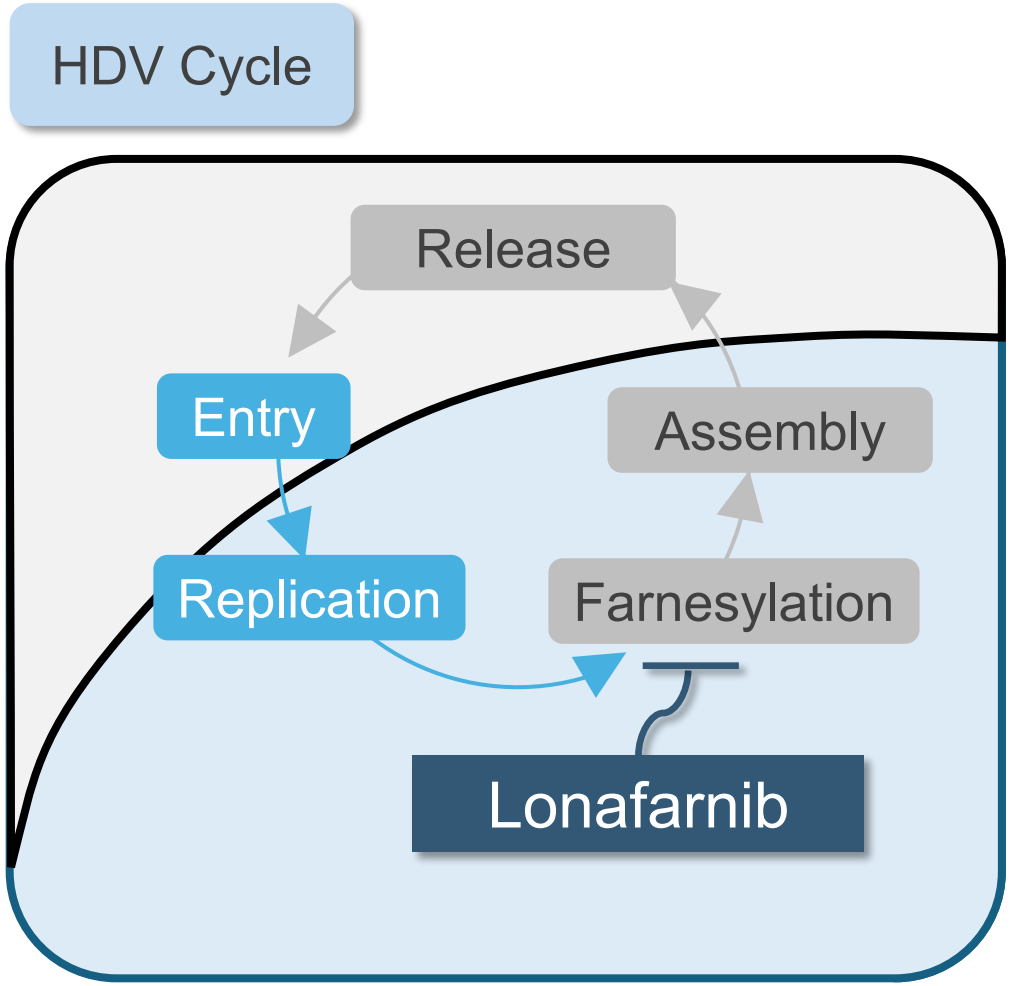
Infective HDV particles consist of HDV ribonucleoproteins in complex with HBV antigens.

Assembly of the HBV:HDV complex requires prenylation of the L-HDAg by host farnesyltransferase.

Lonafarnib (LNF), a farnesyltransferase inhibitor, prevents formation, assembly and release of infective HDV particles[1-3]

This leads to **inhibition of viral release** and **activation of interferon-stimulated genes (ISGs)[4]** that induce immunomodulatory activity.

Lonafarnib directly inhibits viral assembly



1. Glenn, J. S., Watson, J. A., Havel, C. M., et al. (1992). Science, 256(5061), 1331–1333. 2. Otto, J. C., & Casey, P. J. (1996).. Journal of Biological Chemistry, 271(9), 4569–4572. 3. Bordier BB, Ohkanda J, Liu P, et al. Journal of Clinical Investigation. 2003;112(3):407–414. 4. Lempp, F. A., Schlund, F., Rieble, L., et al. (2019). Nature Communications, 10, Article 2265.

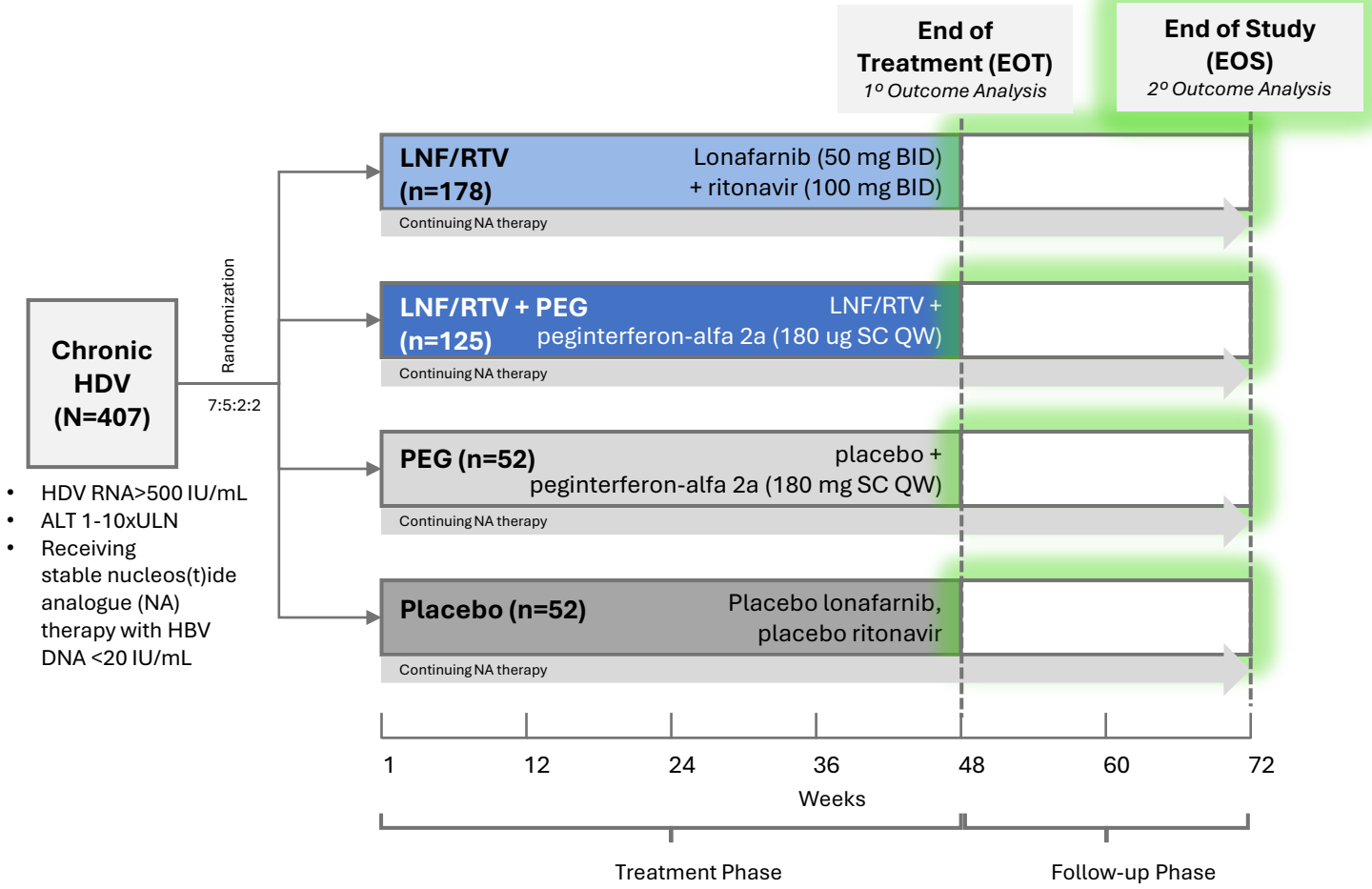
Ph 3 D-LIVR Study was designed to evaluate fixed regimen and off-treatment response to oral Lonafarnib

The D-LIVR study evaluated treatment outcomes at 48 weeks and after a 24-week off-treatment follow-up

D-LIVR is the largest placebo-controlled trial of HDV patients to date (>400 participants in 21 countries)

LNF-based treatment was evaluated against a placebo group.

A PEG monotherapy arm was included to identify safety and efficacy component contributions in combination treatment.

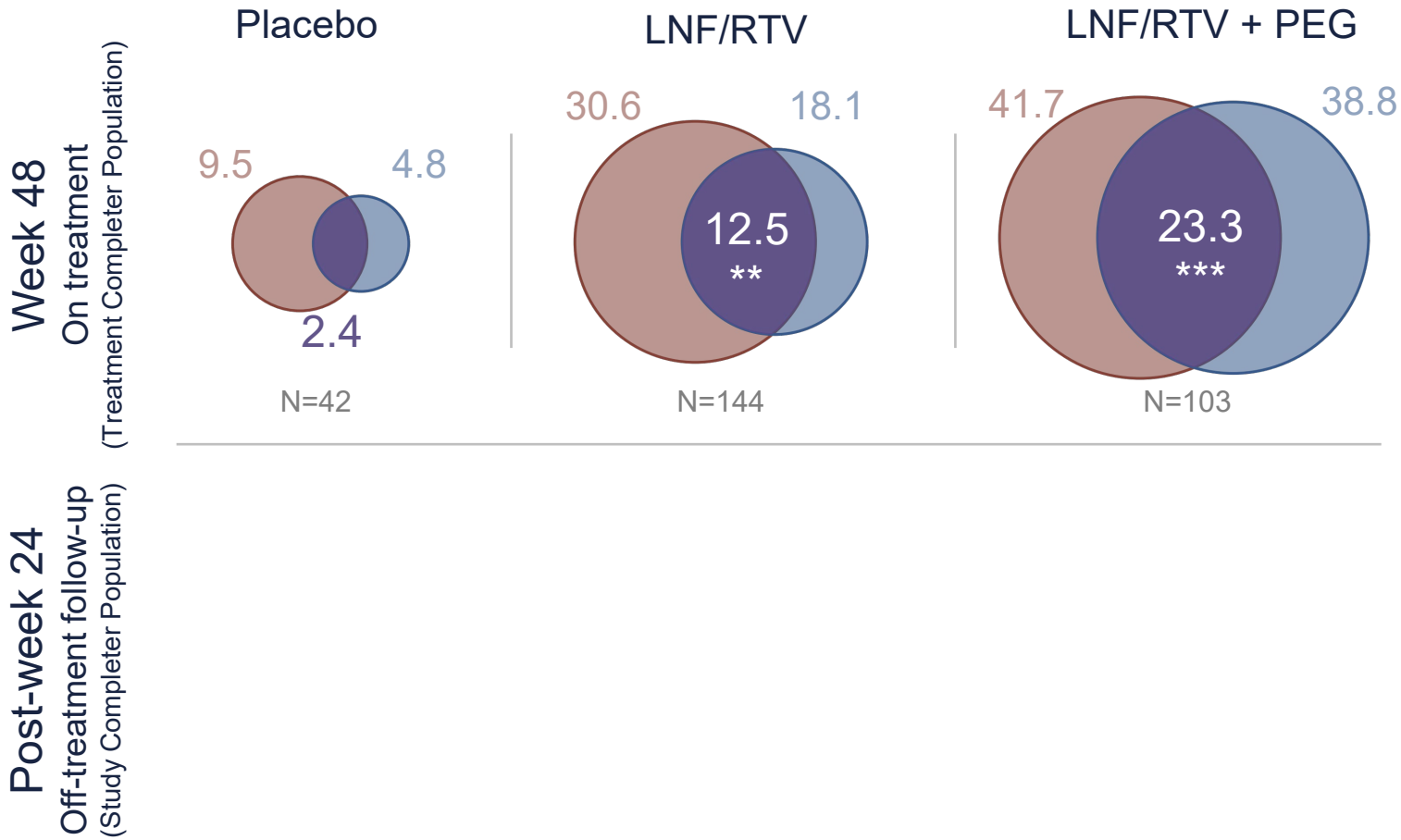


Composite treatment response on- and off-treatment

Lonafarnib treatment achieved significant composite response at Week 48

- **Composite Responders (%)**
  (ALT normalization AND ≥2 log10 reduction in HDV RNA)
- Biochemical responders (%)
  (ALT Normalization)
- Virologic Responders (%)
  (≥2 log10 reduction in HDV RNA)

Significant proportions of patients treated with LNF/RTV both with and without PEG treatment achieved composite virologic and biochemical response at 48 weeks of treatment.



*** p <0.0001, ** p < 0.0.01
Per protocol analysis at Week 48 includes the Completer population (all participants with a Week 48 visit) and at Post-week24 includes EOS completers (all participants with follow-up data of at least 20 weeks.
Week 48 composite response comparing LNF/RTV and LNF/RTV + PEG against placebo was the primary prespecified endpoint for the D-LIVR trial with Bonferonni adjustments to α of 0.03 to LNF/RTV vs Placebo and 0.02 to LNF/RTV + PEG vs Placebo.
Post-week 24 comparisons were a pre-specified secondary endpoint comparing LNF therapies against placebo with an α of 0.05 for each.

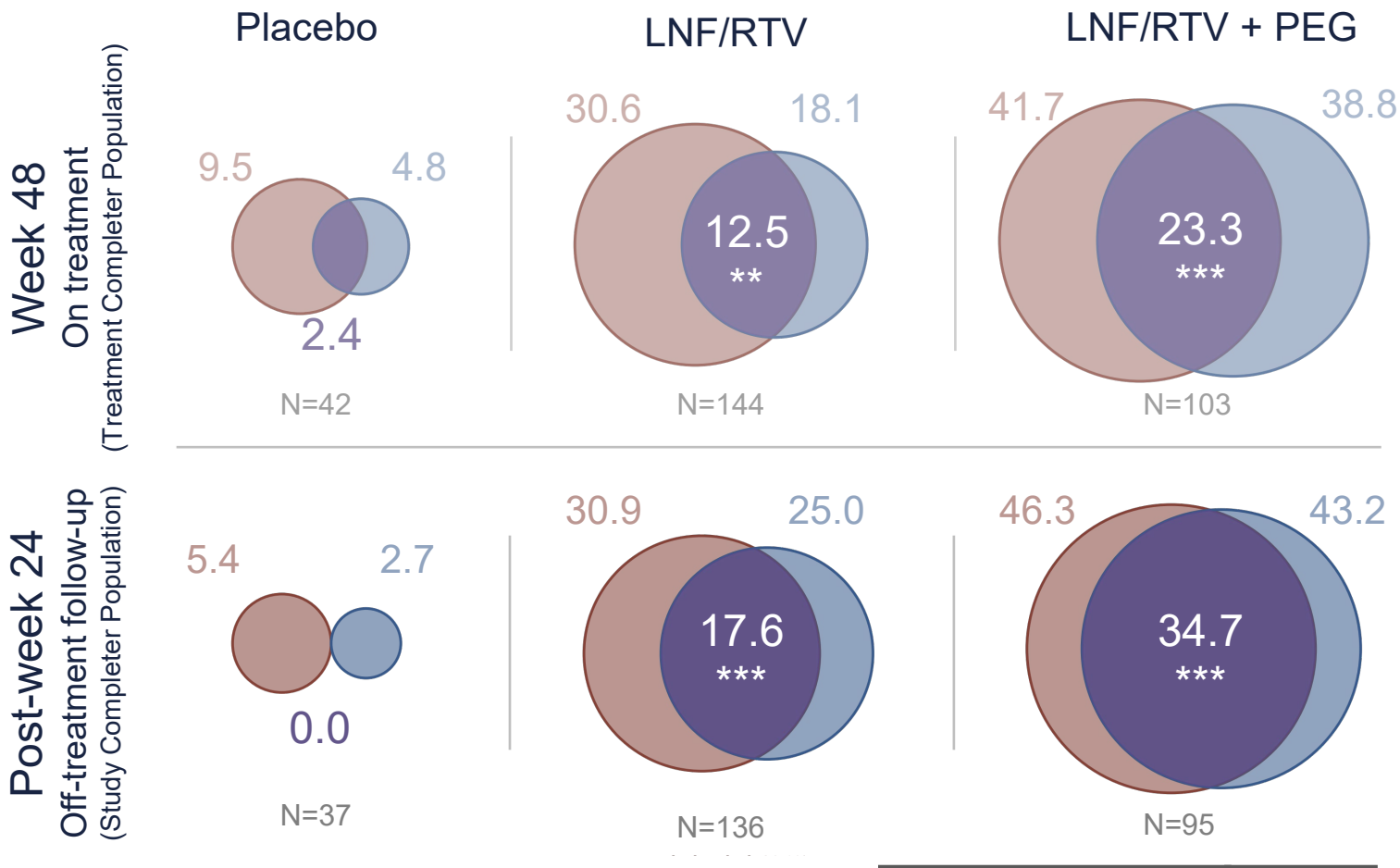
Composite treatment response on- and off-treatment

Composite response was improved after 24-weeks off treatment

Composite Responders (%)
(ALT normalization AND ≥2 log10 reduction in HDV RNA)

Biochemical responders (%)
(ALT Normalization)

Virologic Responders (%)
(≥2 log10 reduction in HDV RNA)



HDV RNA <LLOQ LNF/RTV + PEG at PW 24:	28.4%

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Post-treatment effects driven by durability and new responses



More than 40% of composite responders at end of treatment maintained their response through follow up, and additional patients achieved composite response by end of study

Durability Rate (EOT-EOS)

LNF/RTV:
44.4% Durable
(8 out of 18)

LNF/RTV + PEG:
41.7% Durable
(10 out of 24)

New Response Rate (EOT-EOS)

LNF/RTV:
12.7% New
(16 out of 126 non-responding completers)

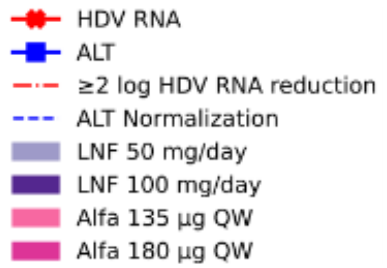
LNF/RTV + PEG:
29.1% New
(23 out of 79 non-responding completers)

Durability of response was evaluated among subjects who achieved composite response (≥2 $\log_{10}$ reduction in HDV RNA and ALT normalization relative to baseline) at Week 48 (End of Treatment [EOT]) and who maintained composite response at 24 weeks post-treatment (End of Study [EOS]). EOS composite response was determined using a per protocol analysis consisting of a completer population, defined as all participants with a Week 48 visit and a simplified last-observation-carried-forward (LOCF): if the Week 24 assessment was missing, the Week 20 post-treatment value was carried forward; if both Week 20 and Week 24 assessments were missing, the subject was classified as not achieving EOS composite response. Newly emergent EOS composite response was evaluated among subjects who did not achieve composite response at Week 48 (End of Treatment [EOT]), but who subsequently met the composite response criteria at 24 weeks post-treatment (End of Study [EOS]).

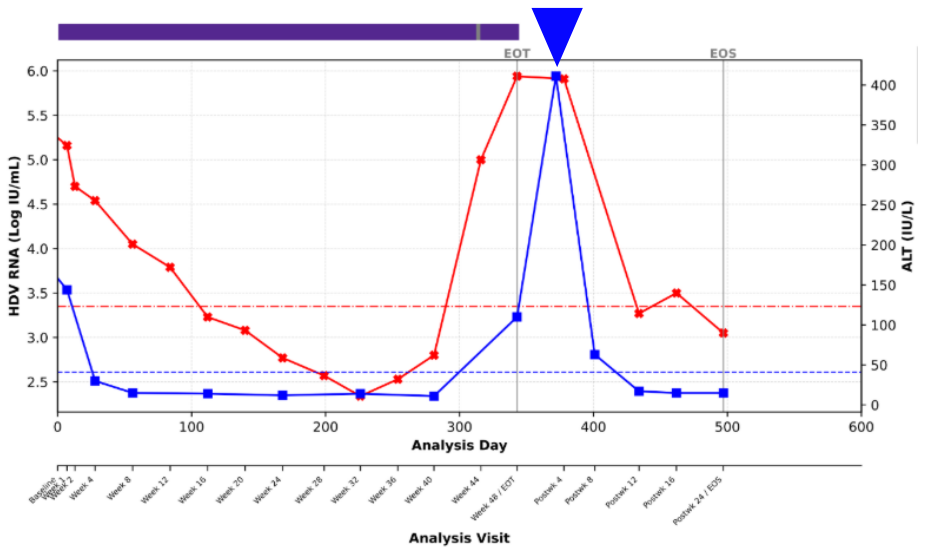
Post-treatment transient ALT elevations in LNF-treated groups

Longitudinal patient profiles with post-treatment ALT elevations

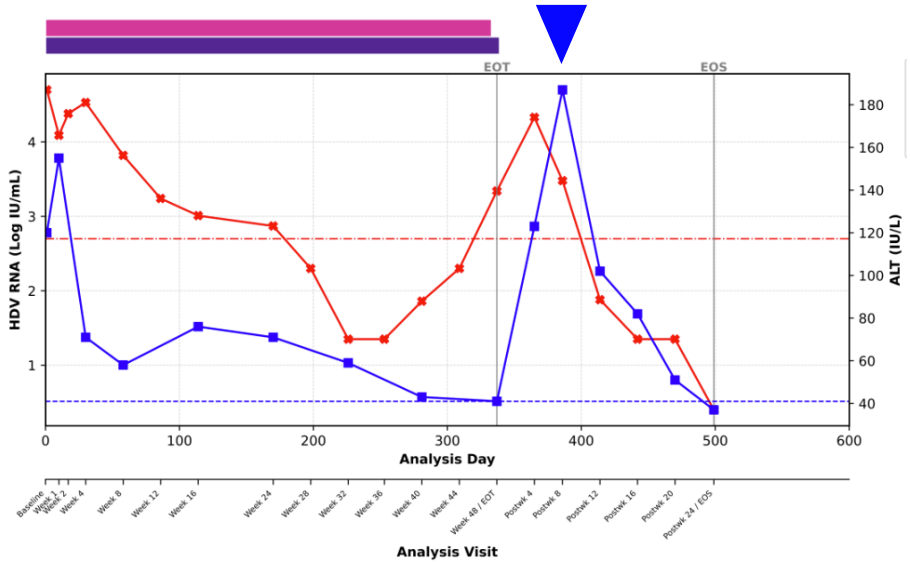
Participants treated with LNF/RTV (left) or LNF/RTV+PEG (right) with evidence of a post-treatment transient ALT elevation (blue arrowhead). In response to the post-treatment ALT elevation, HDV RNA levels (red trace) fall rapidly to achieve a >2 log decline.



Case 1: LNF/RTV



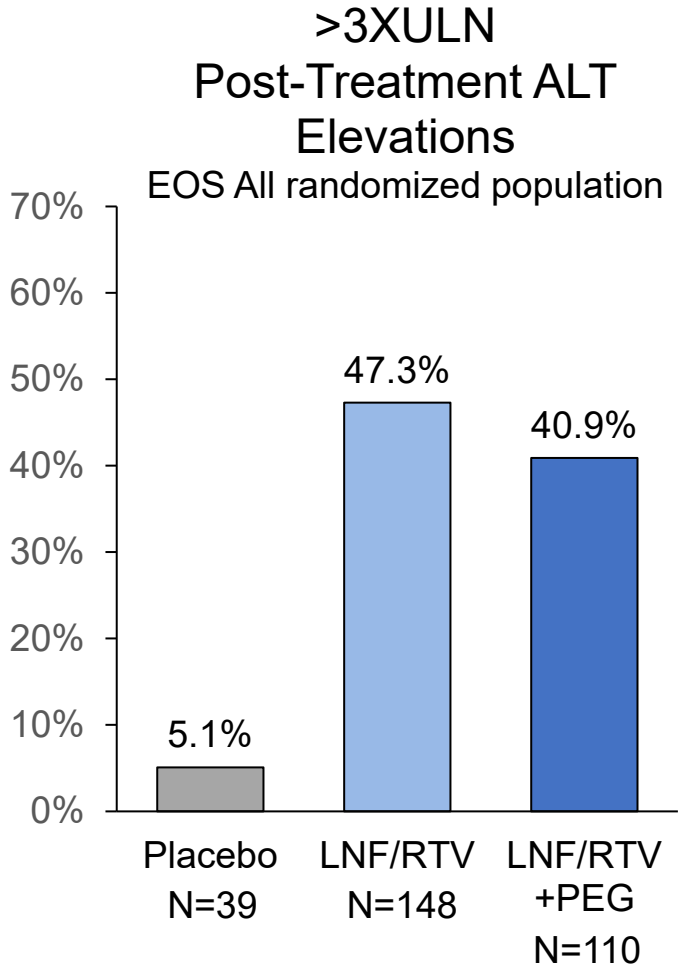
Case 2: LNF/RTV+PEG

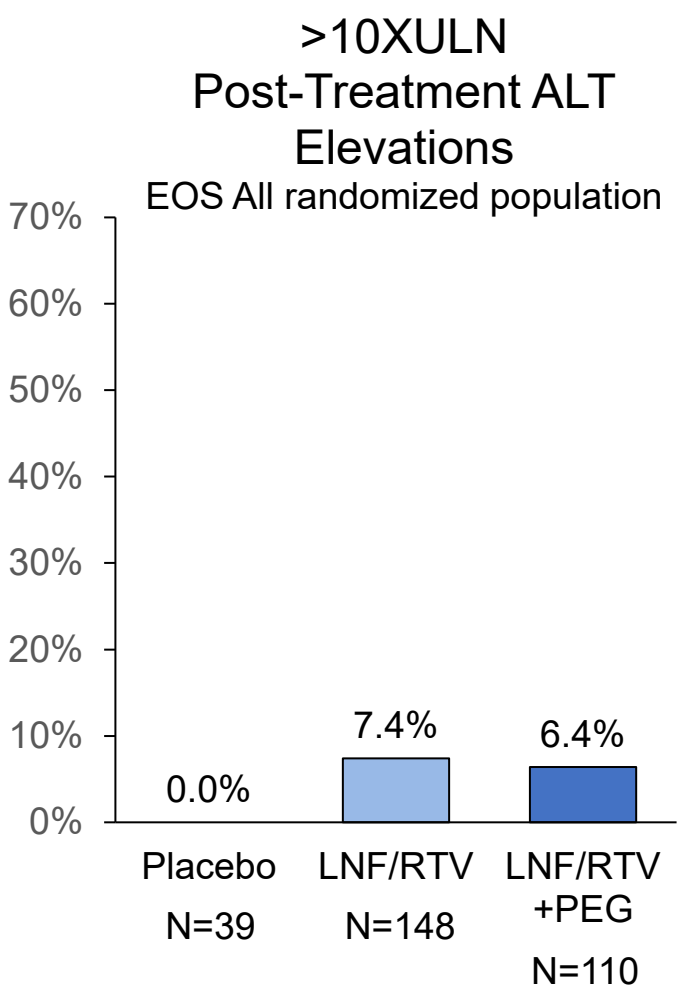


Longitudinal HDV RNA (log_{10} IU/mL, red) and ALT (IU/L, blue) values are plotted by analysis day. LNF dose levels are shown per day, where 100 mg/day corresponds to LNF 50 mg twice daily (BID) and 50 mg/day represents dose reduction to 25 mg BID. Alfa doses are shown per day as indicated in legend.

Abbreviations: Alfa: peginterferon alfa-2a; ALT: alanine aminotransferase; EOS: end of study; EOT: end of treatment; HDV: hepatitis D virus; LNF: lonafarnib; RNA: ribonucleic acid; RTV: ritonavir; Postwk: post-treatment week.

Post-treatment transient ALT elevations in LNF-treated groups





Transient ALT elevations were recorded after cessation of LNF-based treatment

Mild (>3XULN, solid) ALT elevations were recorded in many LNF-treated patients in the post-treatment follow-up period.

Larger ALT elevations (>10XULN, hatched) were more rare, occurring in less than 1 in 10 LNF-treated participants.

No liver decompensation events were recorded in the study, regardless of transient ALT elevations, and the hepatic adjudication committee did not identify DILI events associated with drug treatment.

Posttreatment ALT flare is defined as an ALT measurement > 2 × reference or > 3 × ULN (solid) or >10 × ULN (hatched) occurring between the end of study treatment plus 11 days to the end of off-treatment follow-up, where the reference is the minimum of the baseline and last ALT value up to the end of study treatment plus 10 days.

Post-treatment ALT elevations were associated with decline in HDV RNA

HDV RNA dynamics following transient ALT elevations

	HDV RNA change after ALT elevation (patient counts)	LNF/RTV (N=148)	LNF/RTV + PEG (N=110)
"Host-dominating"	>2 log decline	**10**	**3**
	1 to 2 log decline	**5**	**3**
	0 to 1 log decline	**5**	**1**
	0 to 1 log rise	**1**	**2**
"Virus-dominating"	1 to 2 log rise	0	0
	>2 log rise	0	0

Transient >10XULN ALT elevations occurring after treatment cessation were typically followed by falling HDV RNA

"Host-dominating" ALT elevations are characterized by reduction in viral load[1], a common pattern among LNF-treated participants.

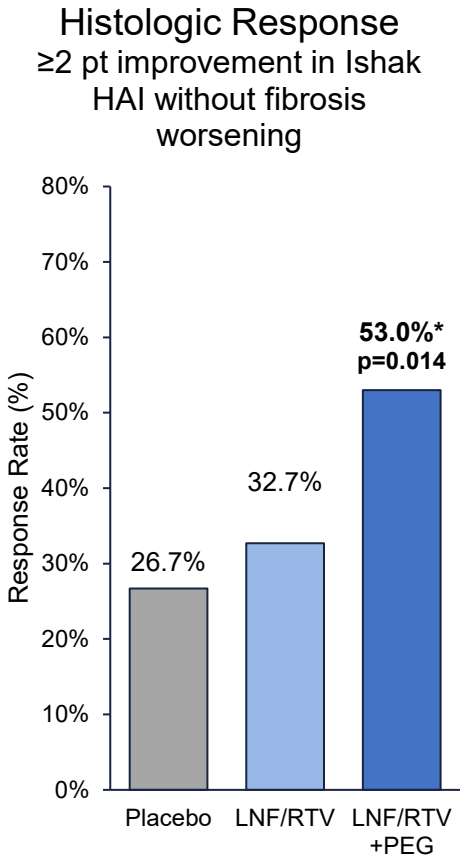
"Virus dominating" ALT elevations are characterized by exacerbation of infection and increased viral load (>1 log rise)[1]. This pattern was not observed among LNF-treated participants

No liver decompensation events were associated with ALT elevations at any point in the study

1: Liaw, Y.-F. (2020). Hepatitis B Flare After Cessation of Nucleos(t)ide Analogue Therapy in HBeAg-Negative Chronic Hepatitis B: To Retreat or Not to Retreat. Hepatology, 73(2), 2021.

ALT elevations in this table are defined as an ALT measurement > 2 × baseline and > 10 × ULN occurring between the start of study treatment and the end of study. HDV RNA change represents change from the reading during the peak of the ALT flare to a reading 12 weeks later.

LNF-based treatment improved histologic endpoint and non-invasive fibrosis measures at Week 48

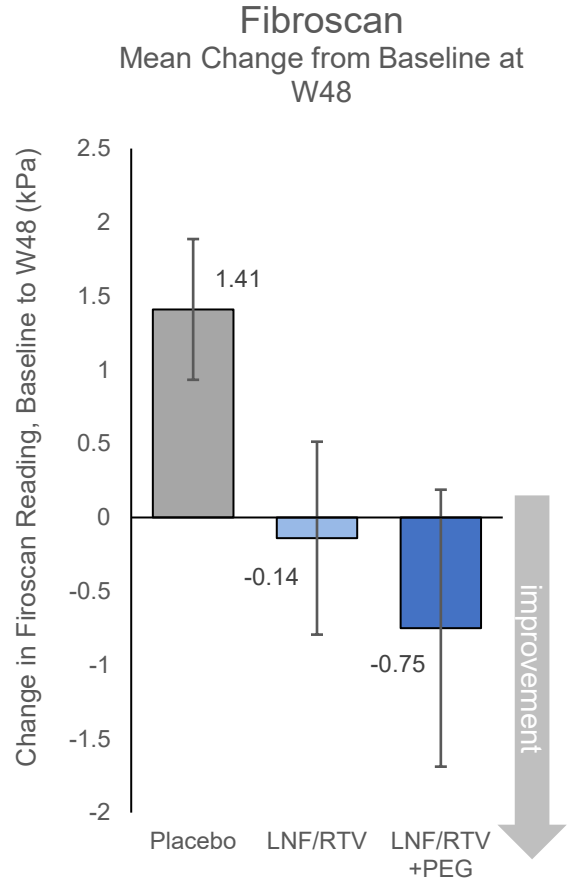


LNF-based therapy improves histology above background HBV therapy

Histology effects were assessed as a secondary endpoint in a large paired biopsy population.
N=229 with evaluable paired biopsies.

This effect is above the background histology benefits all patients experienced due **to background HBV NA therapy**, as most patients initiated NA therapy within 1 year of study start.

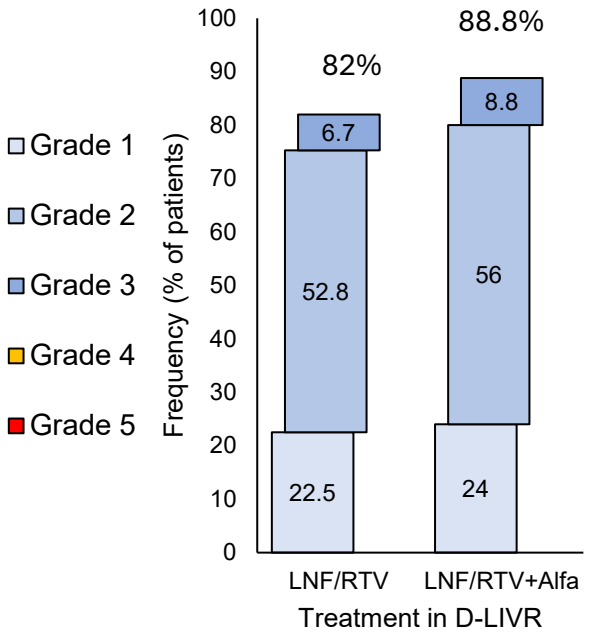
Histologic response pattern is supported by post-hoc analysis of change in FibroScan readings between baseline and Week 48



Histologic response was conducted in a subpopulation with evaluable biopsies at both baseline and Week 48. Biopsies were scored using Ishak HAI criteria by an experienced pathologist blinded to both treatment and timepoint. Liver elasticity was conducted in a separate subset of patients via FibroScan. Group mean change from baseline at Week 48 is presented with error bars representing SEM. The proportion of patients with either improved or unchanged fibrosis by the two methods is presented for comparison.

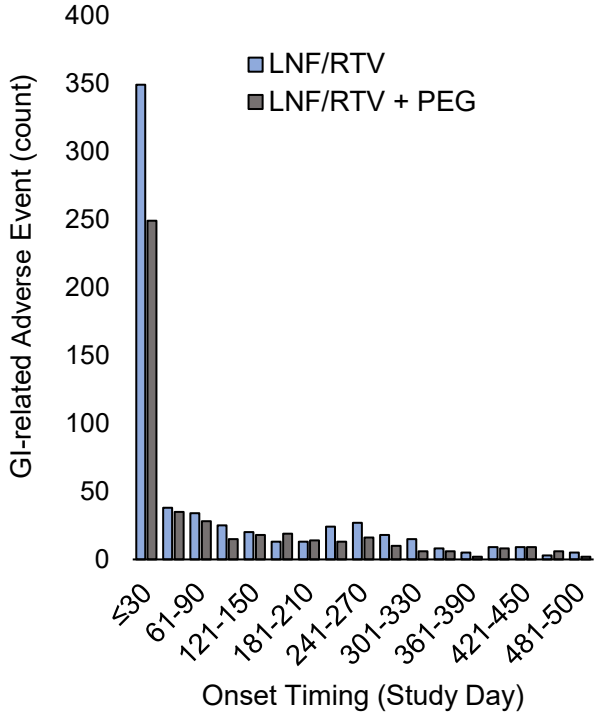
Gastrointestinal tolerability of LNF in D-LIVR

Frequency of GI Disorders



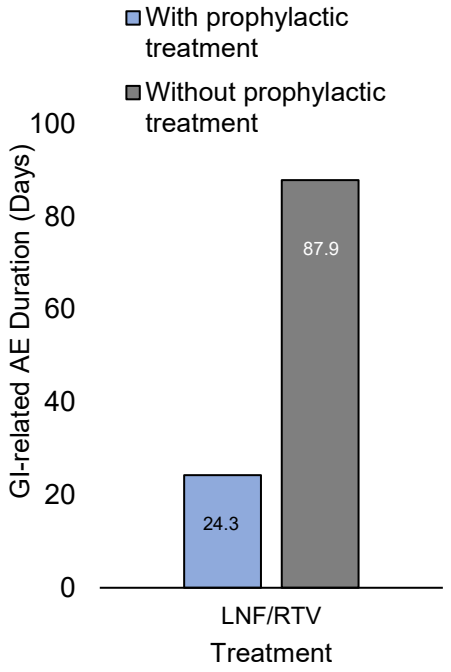
Most LNF-treated participants experienced a **mild or moderate** gastrointestinal adverse reaction

Onset Timing of GI-related Adverse Reactions



The majority of GI adverse reactions **initiated within the first 30 days** of treatment.

Prophylactic treatment reduces GI AE Duration



The duration of GI adverse reactions was reduced by **prophylactic supportive medication**.

GI adverse events in LNF-treated participants were common, moderate, early-onset, and managed with OTC supportive medicines

Supportive medicines used in the trial included, among others:
Loperamide
Ondansentron
Proton pump inhibitors

Summary

- Lonafarnib-based therapies were effective in the large Ph3 D-LIVR study
- Lonafarnib treatment effects were numerically improved during the off-treatment follow-up period
- Composite efficacy at end of treatment was durable in some participants, and some participants achieved the new composite endpoint off-treatment
- Post-treatment transient ALT elevations were observed among LNF-treated participants, and these elevations were associated with HDV RNA decline

- **The totality of evidence favors LNF-based therapy at both Week 48 and after a 24-week off-treatment follow-up**

Thank you to all the participants and investigators who took part in the D-LIVR study