Lonafarnib/ritonavir and peg-interferon alfa drive histological improvement and inflammation resolution in chronic HDV:
results of the multicenter phase 3 D-LIVR study

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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.

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Thinking Innovatively and Operating with Urgency!

HDV Clinical context and unmet medical need

Hepatitis delta virus (HDV) produces severe liver disease

HDV occurs only alongside infection with hepatitis B virus (HBV), and HBV has no curative treatment.
HBV patients who are HDV+ have a 2.2-fold higher risk of liver-related complications

HDV represents a serious unmet medical need

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

The treatment landscape for HDV remains limited

Historically, the standard-of-care for HDV patients is off-label use of peginterferon alfa-2a (PEG).
Bulevirtide (Hepcludex) injections have limited availability and is not yet approved by the US FDA
Lonafarnib remains the only oral HDV treatment option in advanced development.

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Lonafarnib: mechanism of action (MOA)

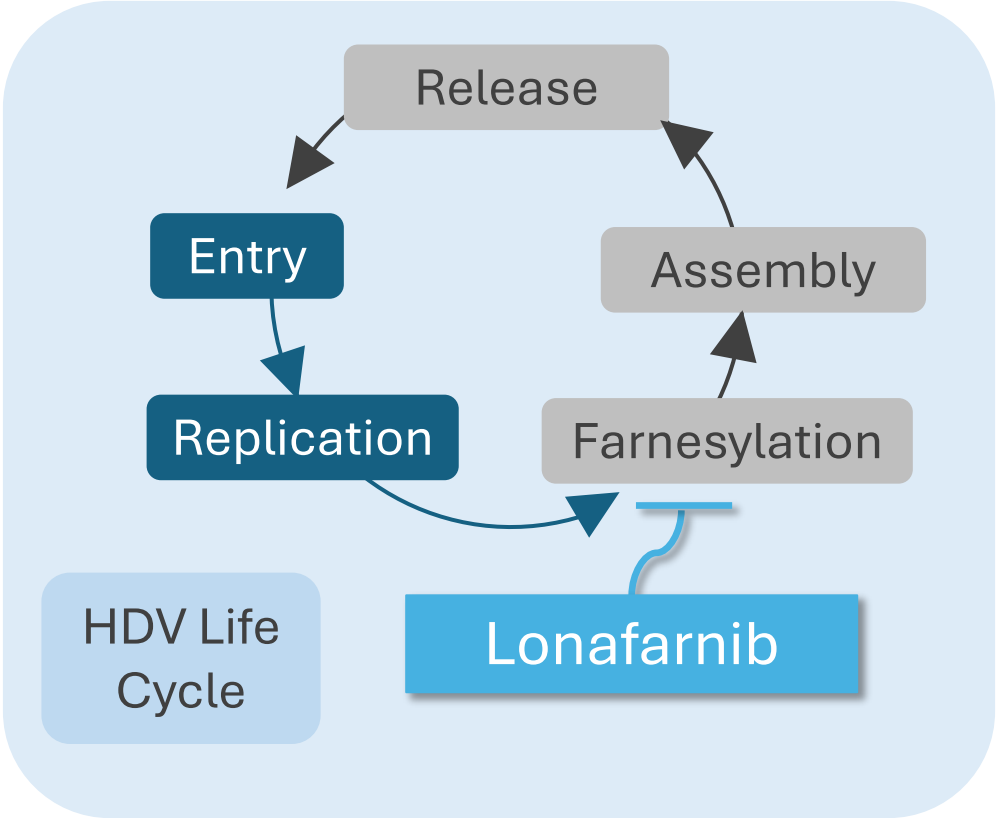
Lonafarnib's unique MOA targets assembly of viral particles preventing formation of infective HDV

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

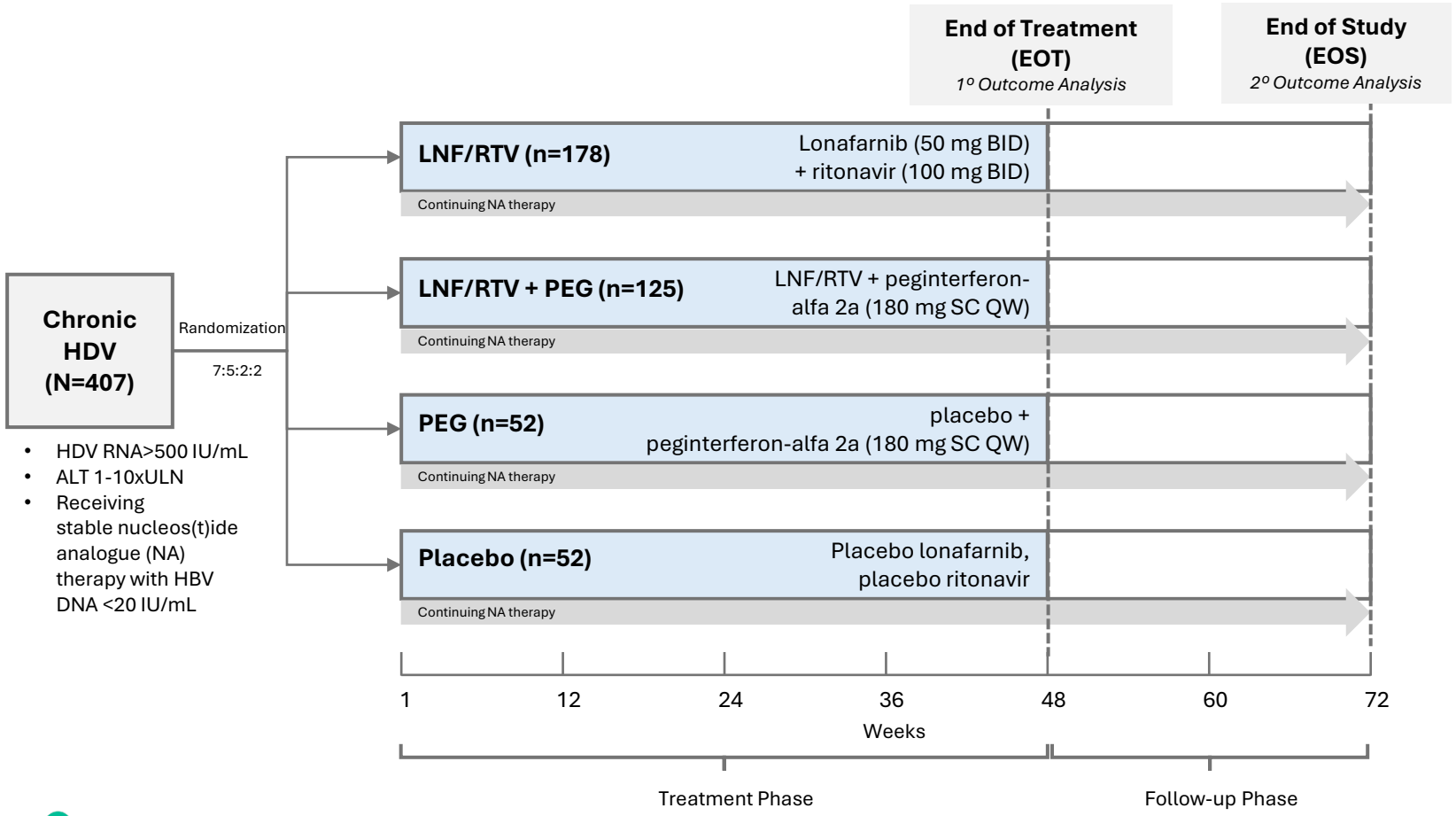
Assembly of the HBV:HDV complex requires prenylation of the L-HDAg by host farnesyltransferase.

Lonafarnib (LNF), a farnesyltransferase inhibitor, prevents formation, assembly and release of infective HDV particles

This leads to intracellular accumulation of viral replicants and activation of interferon-stimulated genes (ISGs) that induce immunomodulatory activity.



D-LIVR study design is powered to evaluate lonafarnib boosted by ritonavir with or with peginterferon alfa-2a



LNF clinical development is supported by a large clinical database (≥2400 pts across indications) **including 4 Phase 2 studies in HDV patients**

The Phase 3 D-LIVR study (EIG-LNF-011) is the largest placebo-controlled trial of HDV patients to date (>400 participants in 21 countries)

The treatment period was 48 weeks with a 24-week off-treatment follow-up period

The objective was to **evaluate efficacy and safety of lonafarnib with ritonavir (LNF/RTV) to boost exposure at low doses either with or without peginterferon alfa-2a (PEG)**.

LNF/RTV ± PEG treatment was evaluated against a placebo group.

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

D-LIVR prespecified study endpoints

Primary	
Composite response at Week 48 on treatment	Defined as: virologic response (≥2 $\log_{10}$ reduction in HDV RNA from baseline) AND Biochemical response (ALT normalization relative to baseline)
Secondary	
At Week 48 on treatment	
Virologic response	≥2 $\log_{10}$ reduction in HDV RNA from baseline
Biochemical response	ALT normalization relative to baseline
Histologic response	improvement in Ishak modified histology activity index (HAI) score of ≥ 2 points relative to baseline and no worsening of fibrosis score relative to baseline
Improved fibrosis	the proportion of patients with improved fibrosis score relative to baseline minus the proportion of patients with worsened fibrosis score relative to baseline
HDV RNA < LLOQ	HDV RNA < Lower limit of quantification (LLOQ), Target detected or Target not detected (TD or TND)
HRQL	Quality of life measured with health-related quality of life (HRQL)
Safety	Safety and tolerability
At 24 Weeks Post-Treatment	
Composite response after 24-week off-treatment follow up	Defined as: virologic response (≥2 $\log_{10}$ reduction in HDV RNA from baseline) AND Biochemical response (ALT normalization relative to baseline)

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D-LIVR study population and baseline characteristics

The study population was well-balanced across arms and representative of global HDV epidemiology

26.5% of the population had cirrhosis at baseline

All study participants took nucleos(t)ide analog (NA) therapy throughout the study to manage HBV coinfection, and most patients initiated NA therapy within 1 year of study start

Characteristic	LNF/RTV	LNF/RTV+PEG	PEG	Placebo	Overall
	n=178	n=125	n=52	n=52	n=407
Age-years (Mean (SD)	42.9 (10.8)	41.4 (11.5)	42.3 (11.0)	45.7 (10.9)	42.7 (11.1)
Male sex (No., %)	126 (70.8)	84 (67.2)	33 (63.5)	39 (75.0)	282 (69.3)
BMI, Mean (SD)	26.4 (4.5)	25.5 (4.7)	25.3 (3.5)	25.7 (3.4)	25.9 (4.3)
Race					
White	130 (73.0)	85 (68.0)	41 (78.8)	42 (80.8)	298 (73.2)
Asian	40 (22.5)	35 (28.0)	10 (19.2)	10 (19.2)	95 (23.3)
Black	3 (1.7)	3 (2.4)	0	0	6 (1.5)
Native Hawaiian or Pacific Islander	3 (1.7)	1 (0.8)	0	0	4 (1.0)
Cirrhosis, No.(%)	47 (26.4)	32 (25.6)	14 (26.9)	15 (28.8)	108 (26.5)
Liver stiffness - kPa, Mean (SD)	12.1 (6.1)	11.5 (5.6)	11.9 (8.3)	13.6 (8.8)	12.1 (6.6)
HDV RNA level - $\log_{10}$ IU/mL, Mean (SD)	4.9 (1.1)	5.1 (1.2)	4.9 (1.2)	4.9 (1.1)	4.9 (1.1)
HDV genotype (No., %)					
1	174 (97.8)	118 (94.4)	52 (100.0)	47 (90.4)	391 (96.1)
4	0	0	0	1 (1.9)	1 (0.2)
5	1 (0.6)	0	0	0	1 (0.2)
8	0	1 (0.8)	0	0	1 (0.2)
Not Determined	3 (1.7)	6 (4.8)	0	4 (7.7)	13 (3.2)
HBsAg level - IU/mL, Mean (SD)	9163.3 (8789.6)	11117.1 (10635.9)	9421.6 (8156.8)	11693.5 (12181.3)	10122.0 (9816.3)
HBeAg Positive (No., %)	178 (100.0)	125 (100.0)	52 (100.0)	52 (100.0)	407 (100.0)
ALT level-U/L Mean (SD)	100.2 (69.1)	99.1 (73.2)	81.9 (46.8)	121.7 (83.3)	100.3 (70.5)
Concomitant HBV Nucleos(t)ide Medication Number (%)	178 (100.0)	125 (100.0)	52 (100.0)	52 (100.0)	407 (100.0)
Duration of therapy (Study day median, SD)	-302 (794.2)	-309 (721.3)	-233 (922.1)	-344 (1569.2)	-297 (922.9)

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LNF treatments achieve composite endpoint at 48 weeks on treatment and after 24-week follow-up

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

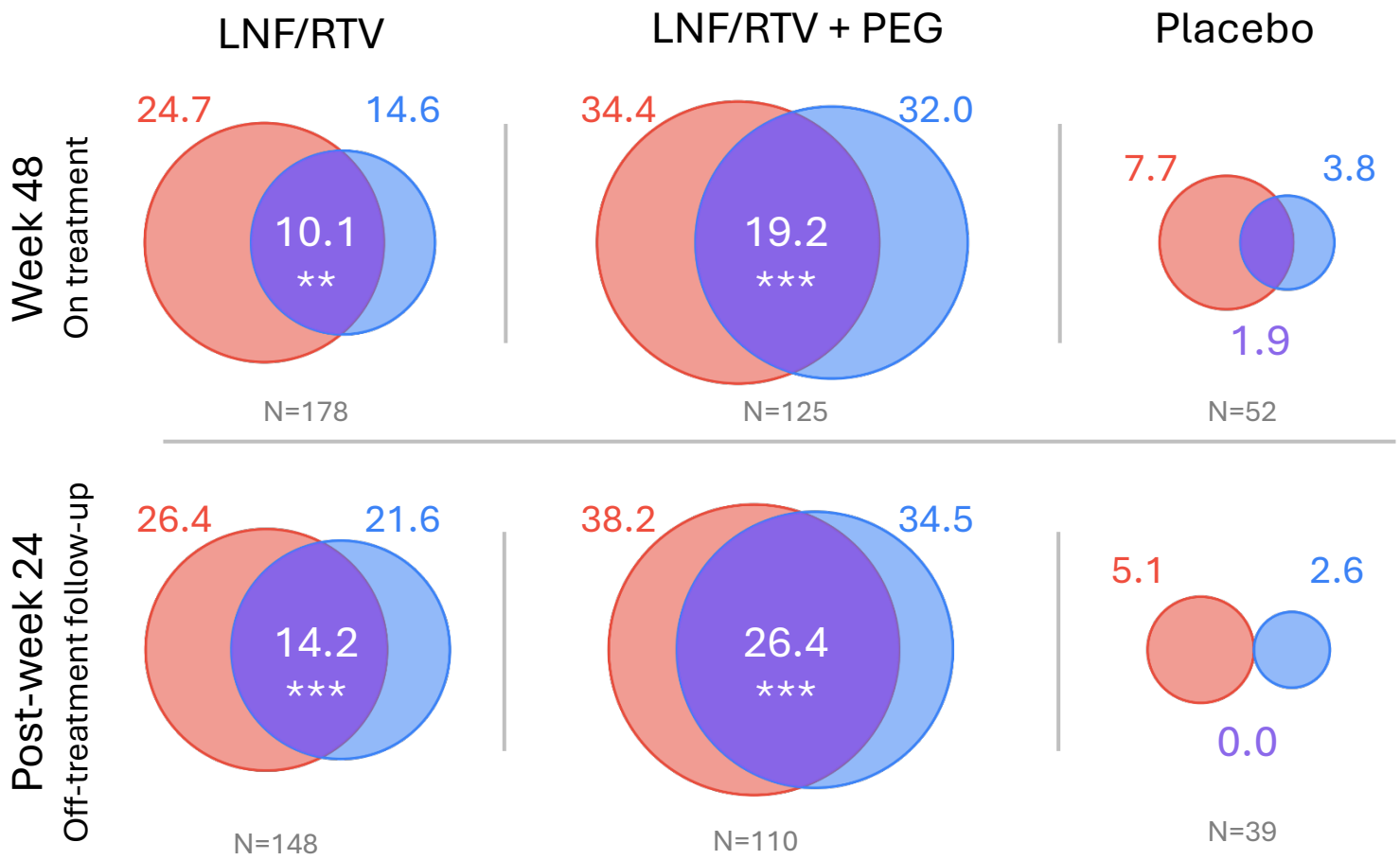
Biochemical responders (%)
(ALT Normalization)

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

Lonafarnib treatment achieves significant composite response

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.

The effect of LNF/RTV ± PEG treatment was still apparent after 24 weeks of off-treatment follow-up.



*** p <0.0001, ** p < 0.0.01
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.

LNF composite response is durable, and new responders emerge during follow-up

On-treatment response to LNF is durable and new treatment response emerges after 24 weeks of off-treatment follow-up

Durability

Over 40% of composite responders in LNF-based treatment arms maintained composite response after a 24-week follow-up period without treatment

New Responders

Some patients who did not achieve composite virologic and biochemical response at the end of the 48-week treatment period achieved composite response during the off-treatment follow-up period.

This effect was particularly strong in the LNF/RTV + PEG treatment group

Treatment	LNF/RTV (n=178)	LNF/RTV + PEG (n=125)	Placebo (n=52)
Durability rate Week 48 composite responders who remained composite responders after 24-weeks off-treatment follow-up % (n/N)	44.4% (8/18)	41.7% (10/24)	0.0% (0/1)
New Responders Week 48 non-responders who achieved composite response after 24-weeks off-treatment follow-up % (n/N)	10% (16/160)	22.8% (23/101)	0.0% (0/51)

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More analyses of durability and speed of response in poster WED-594

Representative patient profiles of durable and post-treatment responders

HDV RNA
ALT
≥2 log HDV RNA reduction
ALT Normalization

Longitudinal patient profiles of durable and new emergent responders

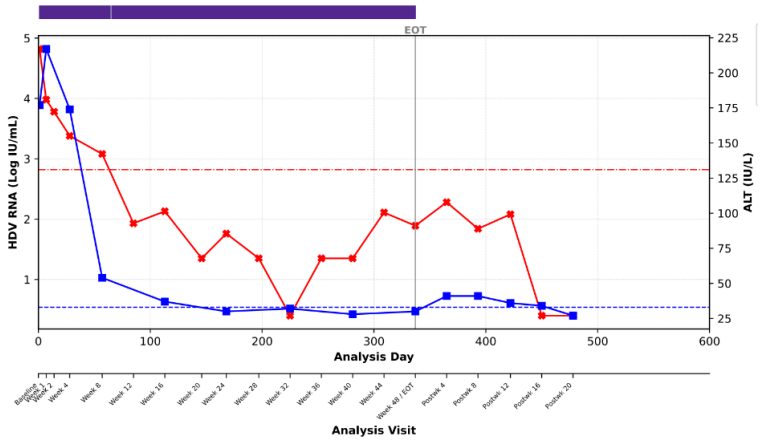
Most patients experience a rapid decline in ALT and HDV RNA in the early treatment period.

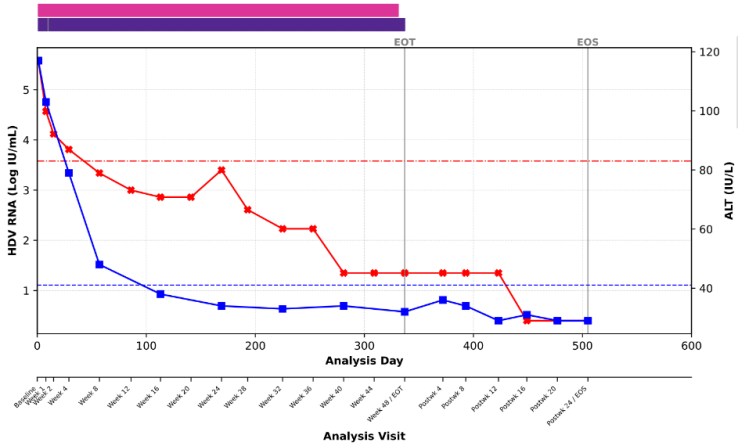
Many patients experience a transient elevation of ALT near or after the end of treatment that corresponds to a sharp reduction in HDV RNA.

LNF/RTV

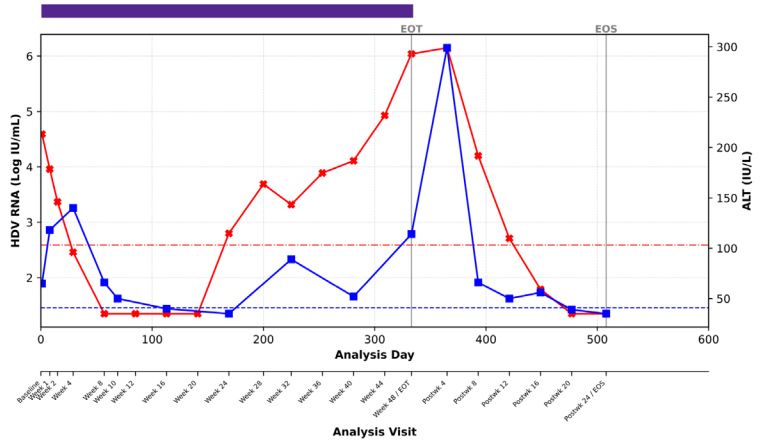
LNF/RTV + PEG

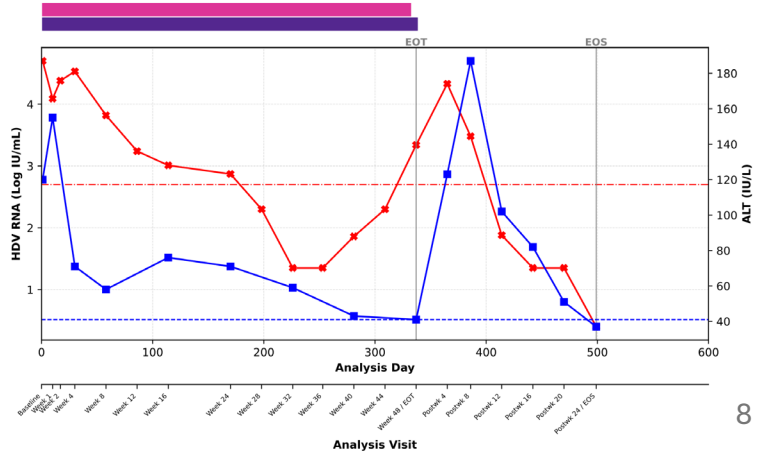
Durable Response





Post-treatment Response





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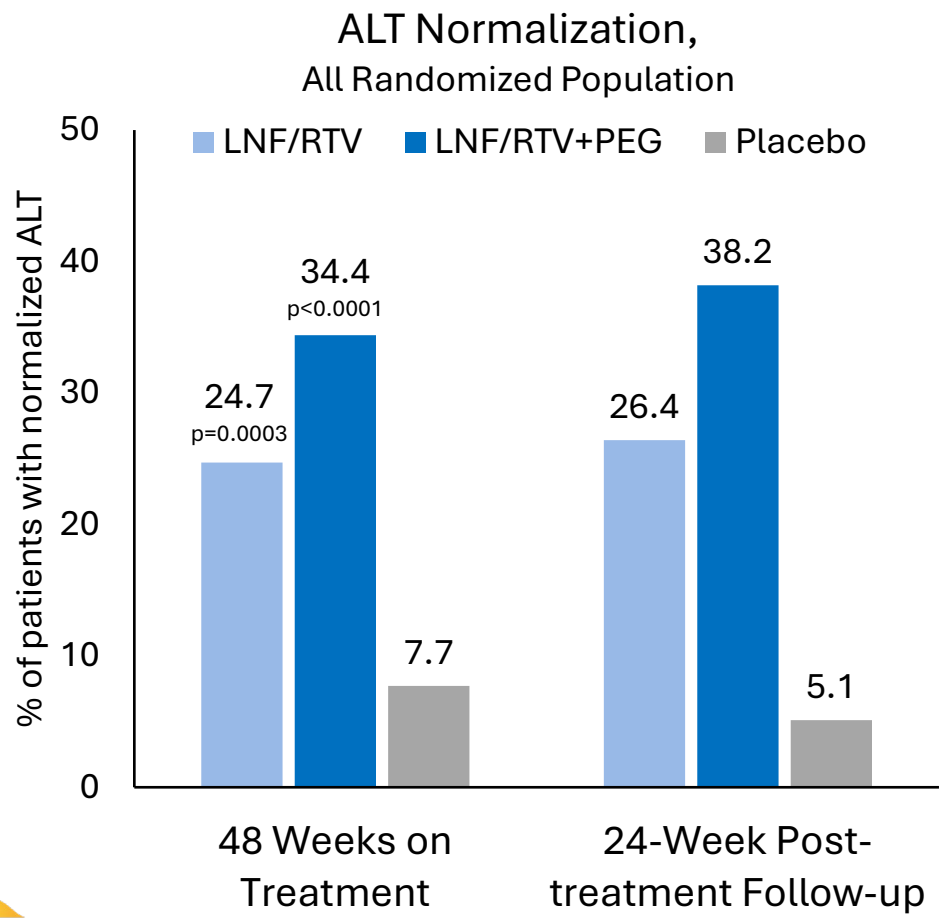
LNF treatment drives ALT normalization



Lonafarnib drives normalization of key indicator of liver inflammation, ALT

93.6% of the overall study population began the study with ALT above the upper limit normal (ULN)

At Week 48 on treatment, approximately **one in 4 patients** treated with LNF/RTV had normalized ALT, while approximately **one in 3 patients** treated with LNF/RTV + PEG combination had normalized ALT.

This ALT normalization effect was still evident after 24 weeks off treatment.

In contrast, the proportion of placebo participants with normalized ALT did not meaningfully change during the study or follow-up period

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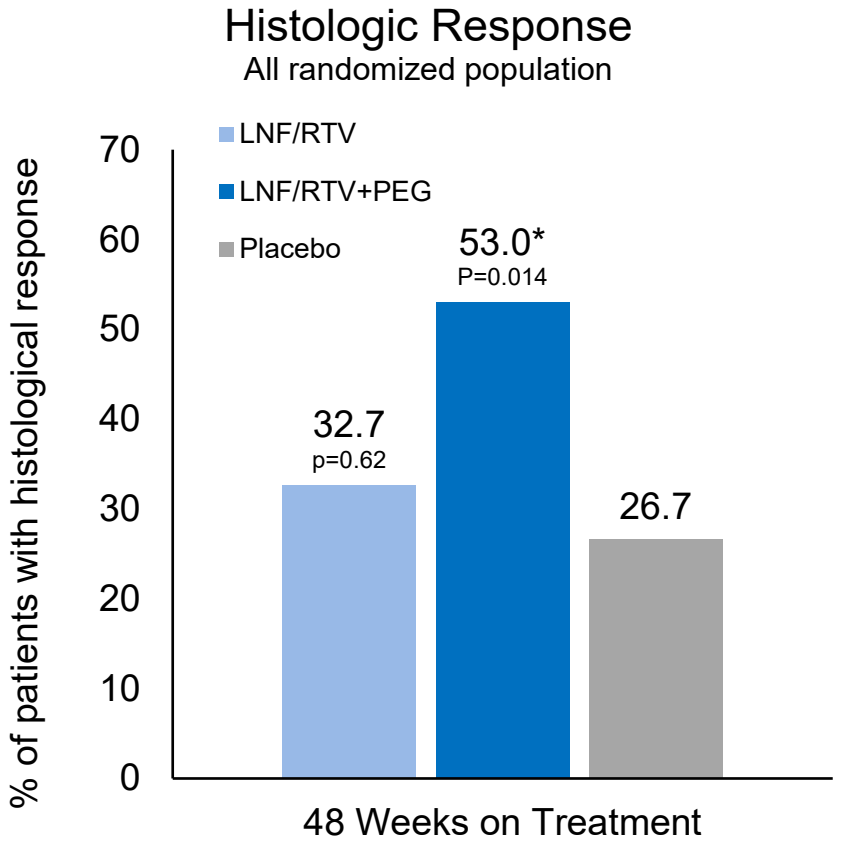
Histology is improved by combination therapy above background HBV treatment



Combination therapy improves histology above background HBV therapy

Histology effects were assessed in a large paired biopsy population.
229 participants had liver biopsies at baseline and at the end of the treatment period (Week 48).

Histological response was defined as a ≥ 2-point improvement in HAI score and no worsening of fibrosis by Ishak score as determined by blinded assessment of paired liver biopsies.

More than 1 in 2 patients in the LNF/RTV + PEG treatment group experienced histological response.

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

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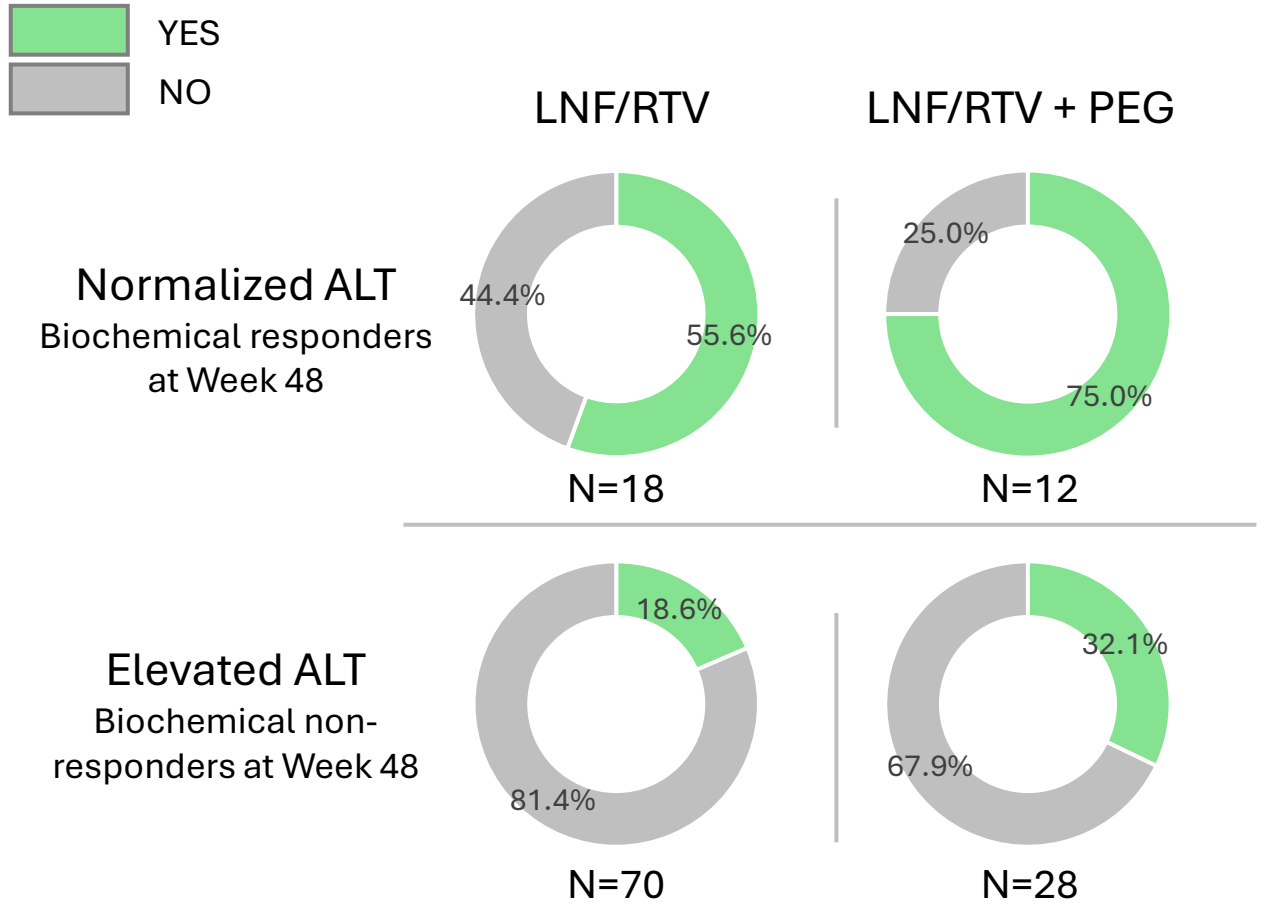
ALT normalization drives histologic improvement even without full virologic repsonse

Histologic response is common among patients with ALT normalization

In the absence of a full virologic response, resolution of inflammation drives histological improvement, likely reflecting a reduction in infection of new hepatocytes.

Histologic Response among patients who did not achieve virologic response

Proportion of histologic responders among viral non-responders



Safety and tolerability profile and management of LNF-based therapy

The safety profile of LNF/RTV ± PEG is predictable, manageable, and clinically acceptable

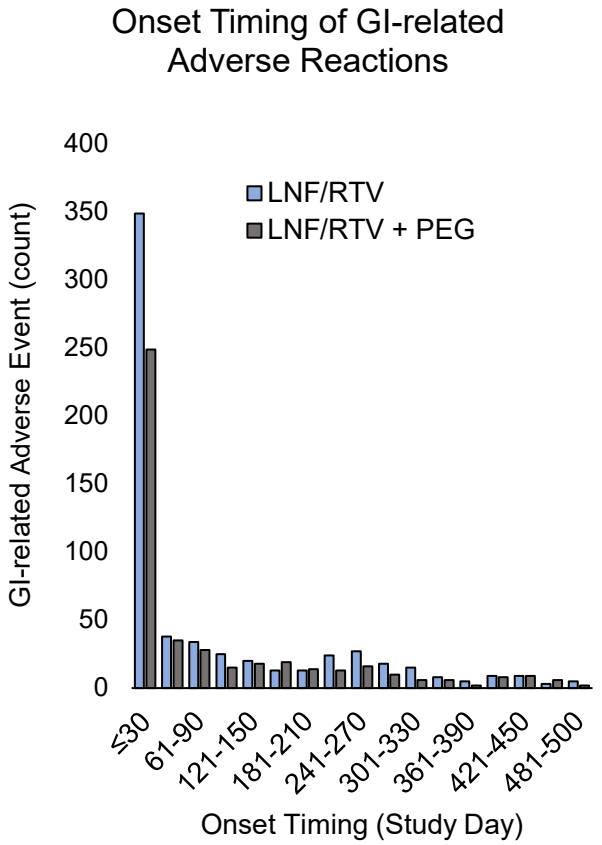
Treatment-emergent adverse events leading to study discontinuation were rare, occurring in only 2.2% of LNF/RTV patients, and no discontinuations among LNF/RTV + PEG or placebo patients.

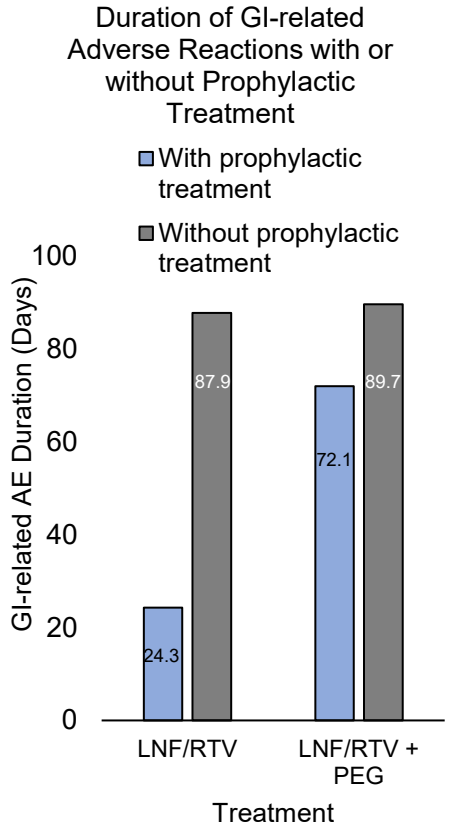
Serious adverse reactions were reported in 8.4% of LNF/RTV patients and 14.4% of LNF/RTV + PEG patients, compared to 3.6% in placebo

Most adverse reactions were mild to moderate gastrointestinal (GI) events

GI adverse reactions typically appeared within the first 30 days of treatment and were managed with temporary dose reduction and/or supportive medication.

Prophylactic use of supportive medication may reduce the duration of GI adverse reactions.





Prophylactic OTC medications to manage GI reactions

Diphenhydramine
Loperamide, Loperamide Hydrochloride
Metoclopramide Hydrochloride
Ondansetron
Ondansetron Hydrochloride
Probiotics

Clinical Interpretation

LNF-based therapies:

- **achieved primary efficacy endpoints** in the large D-LIVR trial of HDV patients, are universally favored over placebo across endpoints, and deliver numerically greater treatment effects after off-treatment follow-up.
- **Normalized ALT, a biomarker of inflammation and** a key driver and prerequisite for histologic improvement.
- **produced histological benefit**, with combination therapy achieving significant improvement in modified Ishak HAI at 48 weeks above background HBV treatment
- promoted inflammation-related histologic benefit even in the absence of full virologic response

These findings support LNF/RTV-based regimens as clinically impactful therapies with the potential to alter the trajectory of HDV.

Lonafarnib is a first-in-class oral HDV therapy with a unique MOA that may form the basis of future combination therapies

More LNF Data at EASL26:

Up to 10 years LTFU data	Speed and Durability
WED-603	WED-594

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