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Poster for you

Histologic improvement and reduction in necroinflammation with lonafarnib-based therapy in chronic hepatitis delta: phase 3 D-LIVR trial

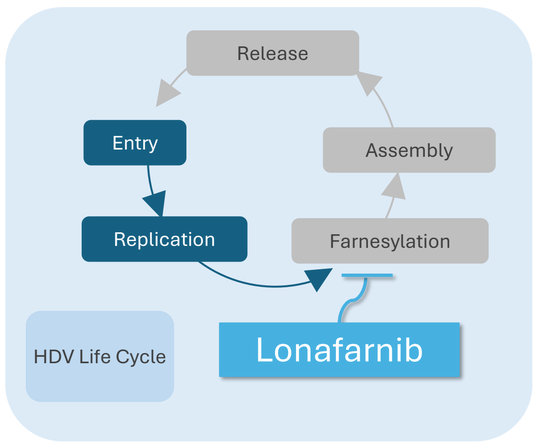
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Introduction

Direct assessment of liver tissue health through collection of paired biopsies is key to distinguishing true antiviral efficacy from fluctuations in biomarkers.



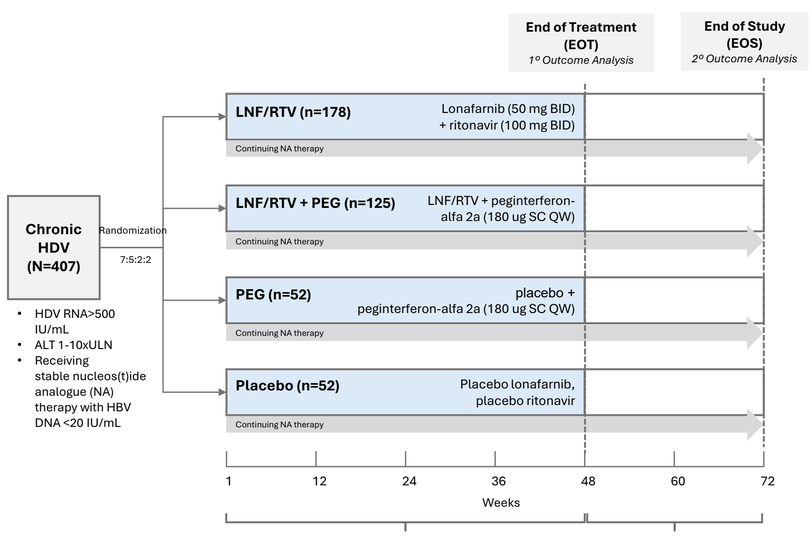
The D-LIVR trial included a large collection (N=229) of paired biopsies to directly assess treatment efficacy.

Lonafarnib (LNF) pharmacokinetically boosted with ritonavir (LNF/RTV) remains the only late-stage oral agent under development for the treatment of chronic hepatitis D virus (HDV) and is being advanced as a 48-week oral treatment for patients living with HDV.

By inhibiting host farnesyltransferase, LNF disrupts HDV virion assembly in infected hepatocytes and promotes immune modulation. LNF/RTV has been evaluated as monotherapy or in combination with peginterferon alfa-2a (PEG).

Study Design

- D-LIVR is a Phase 3 randomized placebo-controlled HDV study (N=407) evaluating LNF/RTV with or without peginterferon alfa-2a (PEG).
- Lonafarnib treatment included oral lonafarnib (LNF) at 50 mg, BID and oral ritonavir (RTV) at 100 mg BID, delivered double-blind. Peginterferon alfa-2a (PEG) was delivered at 180 ug as a weekly SC injection.
- The primary composite endpoint was defined as a ≥ 2 log reduction in HDV RNA and ALT normalization compared to baseline at 48-weeks (end of treatment [EOT]).
- D-LIVR also included a 24-week off-treatment follow-up period to evaluate post-treatment efficacy and safety after treatment cessation (end of study [EOS]).
- The study enrolled over 400 patients from 21 countries randomized in a 7:5:2:2 to the treatment arms outlined below:



Methods

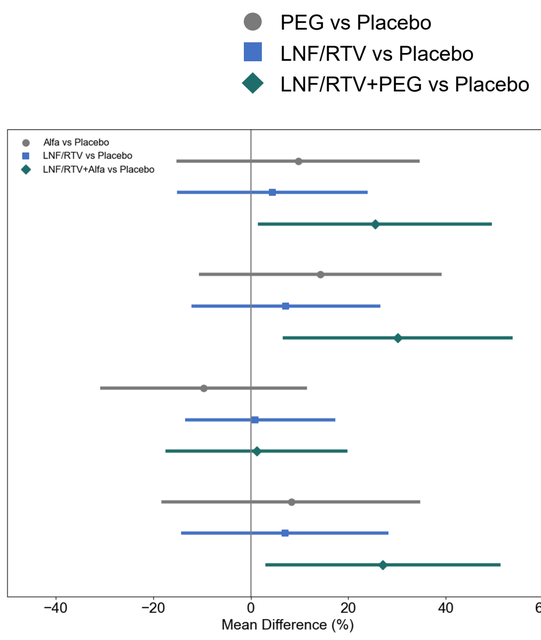
- The primary efficacy endpoint was a composite response rate defined as a ≥ 2 log reduction in HDV RNA and ALT normalization compared to baseline at 48-weeks on-treatment (end of treatment [EOT]).
- D-LIVR also included a large paired-biopsy population (N=229 with baseline and EOT samples collected).
- Liver biopsies were scored using the Ishak Histology Activity Index (HAI)[1] by a liver pathology expert blinded to both treatment and timepoint.
- **The prespecified histologic endpoint was the rate of histologic response compared to placebo with histologic response defined as a ≥2 point improvement in the modified Ishak HAI score without worsening of fibrosis, a rigorous assessment of treatment benefit.**
- Post-hoc analysis of individual Ishak subdomains was conducted to characterize the necroinflammatory nature of tissue changes in response to treatment[2].

Results: Histologic Outcomes

LNF-BASED THERAPIES IMPROVE HISTOLOGIC OUTCOMES AFTER 48-WEEK TREATMENT REGIMEN

- LNF/RTV+PEG treatment resulted in statistically significant improvement in the histologic endpoint (bold p-value). This improvement is above background improvement resulting from universal HBV nucleos(t)ide analog therapy among study participants.
- Compared to placebo, LNF/RTV and LNF/RTV+PEG treatment resulted in directional improvement in histologic endpoints without worsening of Ishak fibrosis scoring.

Figure 1 **Forest Plots of Histologic Outcomes at Week 48 (EOT), Biopsy evaluable population**



	Comparison	Mean Difference (%)	CI	p-value
Histologic (≥ 2 pt Modified HAI without fibrosis worsening)	PEG vs Placebo	9.7	(-15.3, 34.7)	0.448
	LNF/RTV vs Placebo	4.4	(-15.2, 24.0)	0.6247
	LNF/RTV+PEG vs Placebo	25.5	(1.5, 49.5)	**0.0135**
Ishak modified HAI (≥2 Point Improvement)	PEG vs Placebo	14.2	(-10.6, 39.1)	0.2609
	LNF/RTV vs Placebo	7.2	(-12.2, 26.6)	0.4190
	LNF/RTV+PEG vs Placebo	30.1	(6.6, 53.7)	0.0029
Fibrosis Non-Worsening	PEG vs Placebo	-9.7	(-30.9, 11.5)	0.3706
	LNF/RTV vs Placebo	0.9	(-13.5, 17.3)	0.9045
	LNF/RTV+PEG vs Placebo	1.2	(-17.5, 19.8)	0.8831
Ishak modified HAI (≥ 1 Points Improvement)	PEG vs Placebo	8.3	(-18.3, 34.8)	0.5413
	LNF/RTV vs Placebo	7.0	(-14.3, 28.2)	0.4758
	LNF/RTV+PEG vs Placebo	27.1	(3.0, 51.2)	0.0089

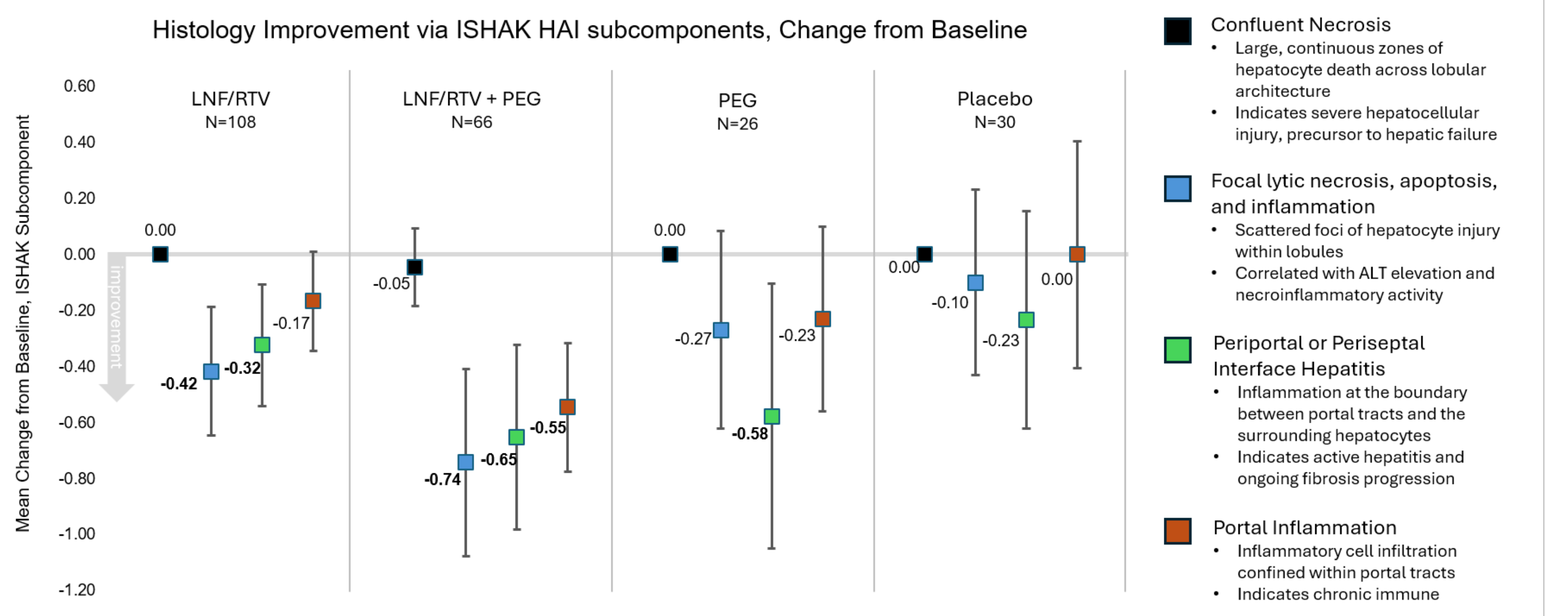
Forest plot shows mean differences versus placebo with corresponding confidence intervals for PEG, LNF/RTV, and LNF/RTV+PEG. Confidence intervals are 95% for PEG versus placebo, 97% for LNF/RTV versus placebo, and 98% for LNF/RTV+PEG versus placebo. Histologic response was defined as a ≥2-point improvement in Ishak modified Histologic Activity Index (HAI) without worsening of fibrosis. Supporting analyses evaluated ≥2-point and ≥1-point improvement in Ishak modified HAI and fibrosis non-worsening. Positive mean differences favor active treatment. HAI = Histologic Activity Index; LNF = lonafarnib; RTV = ritonavir; PEG = peginterferon alfa-2a.

Results: Ishak Subdomains

MEAN CHANGE FROM BASELINE IN HISTOLOGIC MARKERS OF LIVER INFLAMMATION

- Histologic impact of LNF-based therapies was characterized by analysis of group mean change of Ishak subdomains compared to each subdomain mean at baseline. Measures with 95% confidence intervals (error bars) that do not cross the axis are considered nominally significant compared to baseline.
- Subdomain measures that most directly reflect liver tissue inflammation (Focal lytic necrosis, apoptosis, and inflammation [blue] and periportal or periseptal interface hepatitis [green]) were the most strongly impacted by LNF-based therapies

Figure 2 **Change in Mean Ishak Subdomain Scores at Week 48 by Study Treatment, Biopsy evaluable population**



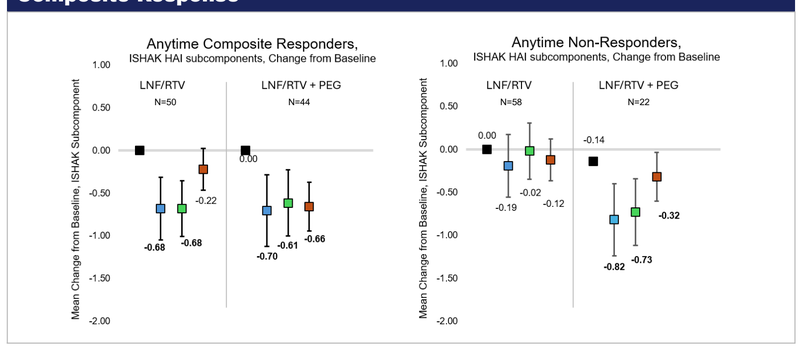
Mean change from baseline in Ishak score among distinct Ishak subcomponents. Squares indicate mean change from baseline and error bars indicate 95% confidence intervals. Subcomponents whose 95% CIs do not cross the axis (bold data labels) can be considered to be nominally significantly changed compared to their own baseline. The Ishak subcomponents are represented as follows: black squares: confluent necrosis, blue squares: focal lytic necrosis, apoptosis, and inflammation, green squares: periportal or periseptal interface hepatitis, red squares: portal inflammation.

Abbreviations: LNF: lonafarnib, PEG: pegylated interferon alfa-2a, RTV: ritonavir

ISHAK INFLAMMATION BY ANY-TIME RESPONSE

- Mean change in Ishak subdomains from baseline was stratified by patients who achieved a composite treatment response (virologic and biochemical) at any time during the study (any-time responders)
- In LNF/RTV-treated patients, inflammatory Ishak subdomain changes are associated with any-time composite response

Figure 3 **Change in Mean Ishak Subdomain Scores Stratified by Anytime Composite Response**



Mean change from baseline in ISHAK score among distinct ISHAK subcomponents stratified by any-time composite response. Anytime responders defined as patients who achieved composite response at any time during the study, regardless of status at EOT. Composite response defined as ≥2 log10 IU/mL decrease in HDV RNA and ALT normalization.
Abbreviations: LNF: lonafarnib, PEG: pegylated interferon alfa-2a, RTV: ritonavir

Conclusions

- Both LNF/RTV and LNF/RTV+PEG achieved the primary composite endpoint in the D-LIVR study.
- In the largest paired biopsy population in an interventional HDV trial to date, combination treatment with LNF/RTV+PEG led to statistically significant improvement in histological response after only 48 weeks of treatment.
- Analysis of Ishak subdomains revealed strong improvement from baseline in necroinflammatory measures in both LNF/RTV and LNF/RTV+PEG treatment groups, and this effect was associated with achievement of composite response at any time during the study.
- Direct histologic improvement after a 48-week regimen of LNF-based treatment supports continued development of LNF as a key emerging treatment

References

1. Ishak, K et al. (1995) Histological grading and staging of chronic hepatitis. *Journal of Hepatology.* 22, 69-99.
2. Mannan, R et al. (2014) A comparative evaluation of scoring systems for assessing necroinflammatory activity and fibrosis in liver biopsies of patients with chronic viral hepatitis. *Journal of Clinical and Diagnostic Research.* 8 (8).

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.