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Poster for you

Post-treatment response following 48 weeks of lonafarnib therapy: analysis of 24-week follow-up in the phase 3 D-LIVR trial in chronic hepatitis delta

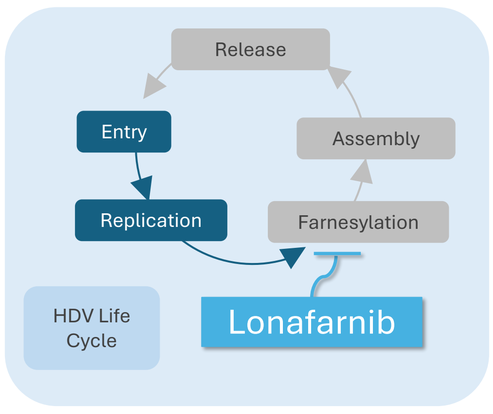
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EIT PHARMA
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Introduction

The durability of treatment response following therapy cessation remains an important consideration in the management of chronic hepatitis D virus (HDV) infection, especially as approved HDV therapies cannot currently be safely stopped[1].

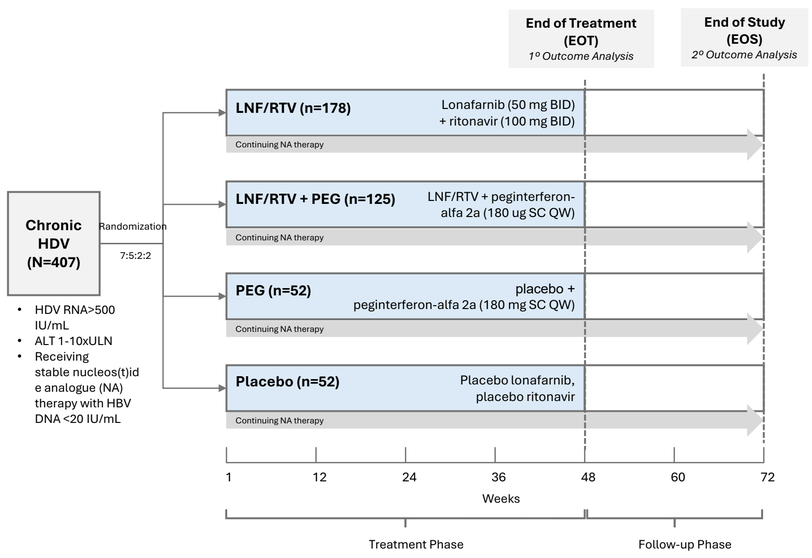


Lonafarnib (LNF) pharmacokinetically boosted with ritonavir (LNF/RTV) remains the only late-stage oral agent under development for the treatment of chronic hepatitis D virus (HDV) and is being advanced as a 48-week oral treatment for patients living with HDV.

By inhibiting host farnesyltransferase, LNF disrupts HDV virion assembly in infected hepatocytes, promotes immune modulation[2-4] and has been clinically 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 both 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:

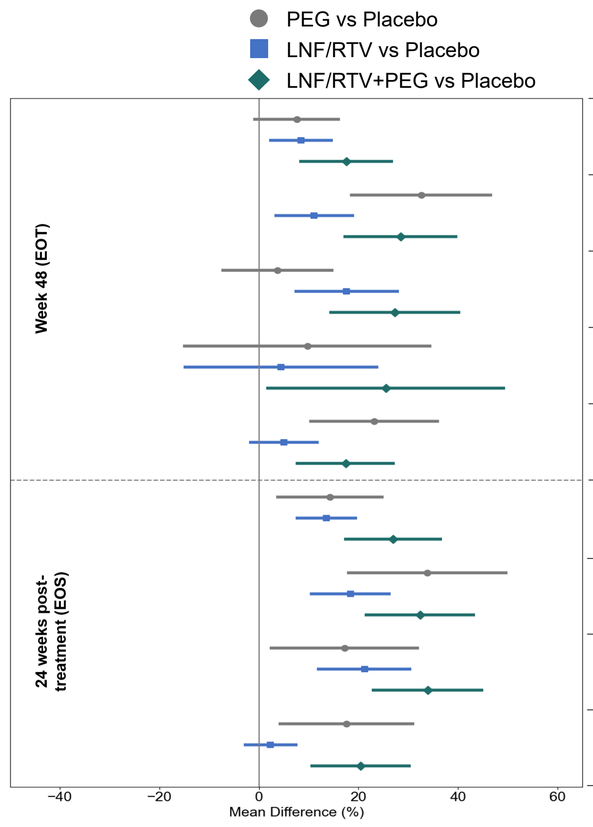


Methods

- 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]).
- Secondary endpoints included component virologic and biochemical responses and histological response at EOT.
- Exploratory endpoints included HDV RNA viral loads below the limit of quantification (<LLOQ, target detected and target not detected) and assessment of endpoints after a 24-week off-treatment follow-up period.
- Durability of treatment effect was assessed as the percentage of patients with treatment response at both EOT and EOS.
- New composite responses were defined as patients who achieved a composite response at EOS among patients who were not composite responders at EOT.
- HDV RNA viral loads were assessed by quantitative RTPCR assay with a lower limit of quantification of 50 IU/mL.

Results: Consistency of Effect

Figure 1 **Forest Plot of Efficacy Endpoints Measured in the D-LIVR Trial Demonstrating Consistency of Effect**



	Comparison	Mean Difference (%)	CI	p-value
Composite – *Primary Efficacy Endpoint* (≥ 2 log HDV RNA reduction and ALT normalization)	PEG vs Placebo	7.6	(-1.2, 16.3)	0.0903
	LNF/RTV vs Placebo	8.4	(2.0, 14.8)	**0.0044**
	LNF/RTV+PEG vs Placebo	17.6	(8.1, 27.0)	**<0.0001**
Virologic (≥2 log HDV RNA reduction)	PEG vs Placebo	32.6	(18.3, 46.9)	<0.0001
	LNF/RTV vs Placebo	11.1	(3.1, 19.1)	**0.0026**
	LNF/RTV+PEG vs Placebo	28.5	(17.0, 39.9)	**<0.0001**
Biochemical (ALT normalization)	PEG vs Placebo	3.7	(-7.6, 15.0)	0.522
	LNF/RTV vs Placebo	17.6	(7.1, 28.1)	**0.0003**
	LNF/RTV+PEG vs Placebo	27.3	(14.1, 40.5)	**<0.0001**
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**
HDV RNA <LLOQ (Target detected and Target not detected)	PEG vs Placebo	23.1	(10.1, 36.2)	0.0005
	LNF/RTV vs Placebo	5.0	(-2.0, 12.0)	0.1194
	LNF/RTV+PEG vs Placebo	17.4	(7.4, 27.3)	<0.0001
Composite (≥ 2 log HDV RNA reduction and ALT normalization)	PEG vs Placebo	14.3	(3.5, 25.1)	0.0093
	LNF/RTV vs Placebo	13.5	(7.4, 19.7)	<0.0001
	LNF/RTV+PEG vs Placebo	26.9	(17.1, 36.8)	<0.0001
Virologic (≥2 log HDV RNA reduction)	PEG vs Placebo	33.8	(17.7, 50.0)*	NC
	LNF/RTV vs Placebo	18.4	(10.2, 26.5)*	NC
	LNF/RTV+PEG vs Placebo	32.4	(21.3, 43.4)*	NC
Biochemical (ALT normalization)	PEG vs Placebo	17.2	(2.2, 32.2)*	NC
	LNF/RTV vs Placebo	21.2	(11.7, 30.6)*	NC
	LNF/RTV+PEG vs Placebo	33.9	(22.7, 45.1)*	NC
HDV RNA <LLOQ (Target detected and Target not detected)	PEG vs Placebo	17.6	(4.0, 31.2)*	NC
	LNF/RTV vs Placebo	2.3	(-3.1, 7.7)*	NC
	LNF/RTV+PEG vs Placebo	20.4	(10.4, 30.5)*	NC

Forest plot demonstrating consistency of treatment effects across composite, virologic, biochemical, and histologic endpoints. Treatment effects for LNF/RTV (blue squares) and LNF/RTV+PEG (green diamonds) consistently favor active therapy over placebo across endpoints, with larger effect sizes observed for the combination regimen. PEG monotherapy (grey circles) outcomes are presented descriptively for comparison, with nominal p-values. Mean differences versus placebo are presented as percentages; p-values are relative to placebo. Week 48 (End of Treatment, EOT) analyses were conducted in the All Randomized (ITT) population. Week 24 post-treatment (End of Study, EOS) analyses were conducted in the EOS-All Randomized population, as prespecified in the SAP. Unless otherwise specified, all responses are assessed relative to baseline. The composite response is defined as ≥2 $\log_{10}$ reduction in HDV RNA and ALT normalization. Virologic response is defined as ≥2 $\log_{10}$ reduction in HDV RNA. Biochemical response is defined as ALT normalization. HDV RNA <LLOQ includes both target detected and target not detected. Histologic response is defined as ≥2-point improvement in Ishak HAI without fibrosis worsening. p values shown in bold correspond to prespecified hierarchical testing and met the allocated alpha levels (97% CI for LNF/RTV vs placebo comparisons; 98% CI for LNF/RTV+PEG vs. placebo comparisons). All non-bold p-values are nominal and include those within the hierarchical sequence that did not meet the allocated alpha, as well as those not formally tested due to the predefined testing order. Comparisons of peginterferon alfa-2a (PEG) are presented with 95% CIs and nominal p-values. Virologic and biochemical responses at 24 weeks post-treatment were predefined exploratory endpoints and were not included in the hierarchical testing framework. For these endpoints, 95% confidence intervals (marked with *) are presented, and p-values were not calculated (NC); based on the 95% confidence intervals, treatment differences would be considered nominally statistically significant.

TOTALITY OF EVIDENCE

Efficacy assessments consistently favored lonafarnib-based treatment regimens both on-treatment and after a 24-week follow-up.

Combination of LNF with pegIFN produced additive efficacy effects that persisted through off-treatment follow-up

Results: Durability and New Responders

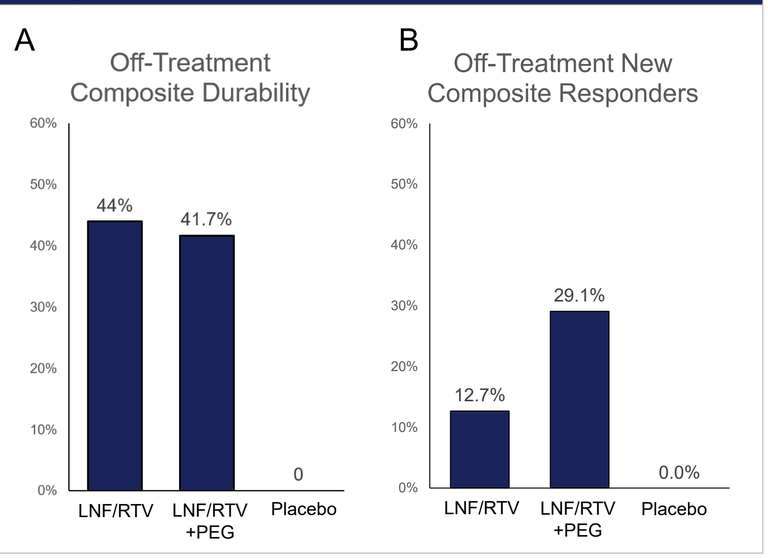
DURABILITY

EOT composite responses were durable through EOS in 44.4% and 41.7% of EOT composite responders in the LNF/RTV and LNF/RTV + PEG treatment arms, respectively (Figure 2A).

NEW RESPONDERS

Among patients who were not composite responders at EOT, newly emergent composite response was achieved in 12.7% of the LNF/RTV treatment group and 29.1% of the LNF/RTV + PEG treatment group (Figure 2B)

Figure 2 **Durability Rate and Emergence of New Responders During Follow-up**



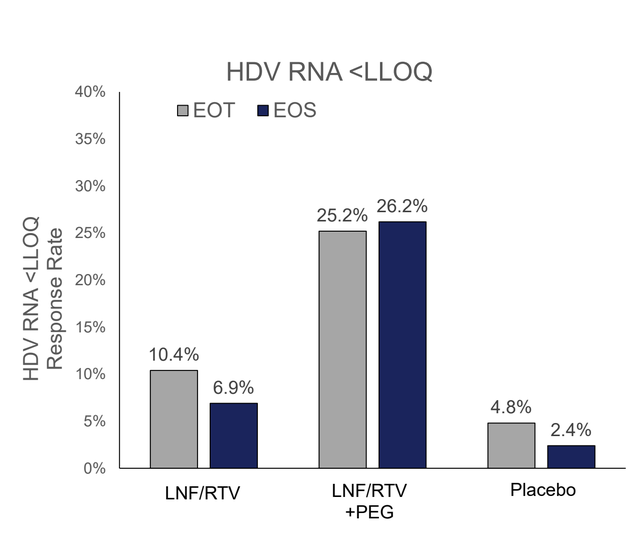
Durability of response was evaluated among subjects who achieved composite response (≥2 $\log_{10}$ reduction in HDV RNA and ALT normalization relative to baseline) at Week 48 (End of Treatment [EOT]) and who maintained composite response at 24 weeks post-treatment (End of Study [EOS]). EOS composite 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]).

Results: Viral Loads Below Quantification Limit

HDV RNA <LLOQ

Viral suppression was stronger in the LNF/RTV + PEG combination group, with HDV RNA <LLOQ achieved in 25.2% (26 of 110) of patients at EOT and 22.7% (25 of 110) of patients at EOS, 50% of which were durable from EOT. HDV RNA <LLOQ was achieved in 10.4% (15 of 144) LNF/RTV patients at EOT and 6.3% (9 of 144) at EOS, 20% of which represent durable response. Corresponding rates in the placebo group were 4.8% (2 of 42) at EOT and 2.4% (1 of 42) at EOS.

Figure 3 **Rates of Patients with HDV RNA below the Limit of Quantification by Treatment and Timepoint**



HDV RNA levels were determined by quantitative RTPCR assay with a lower limit of quantification of 50 IU/mL and a lower limit of detection of 5 IU/mL. The response rate for HDV RNA <LLOQ includes participants with HDV RNA readings below the limit of quantification, both detected and not detected. The response rates are presented as simple percentages of patients. This analysis was performed with per protocol analysis, defined as any participant in the All Randomized population with a Week 48 visit and with EOS status determined by simplified LOCF with Week 20 posttreatment values carried forward if Week 24 posttreatment values were missing.

Conclusions

- Oral LNF/RTV is a first-in-class HDV therapy with efficacy and safety in HDV patients and substantial benefit after treatment cessation.
- All efficacy assessments favor LNF-based treatments and combination treatment with PEG produced additive efficacy signal.
- Among patients treated with LNF/RTV or LNF/RTV + PEG composite treatment response after a 48-week treatment course was durable through a 24-week follow-up in >40% of patients, and some patients who were not composite responders at the end of treatment became composite responders off-treatment.
- Both LNF/RTV and LNF/RTV+PEG produced HDV RNA viral loads below the limit of quantification.

References

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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.