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Poster for you

Clinical significance of ALT dynamics following lonafarnib treatment cessation in the phase 3 D-LIVR trial

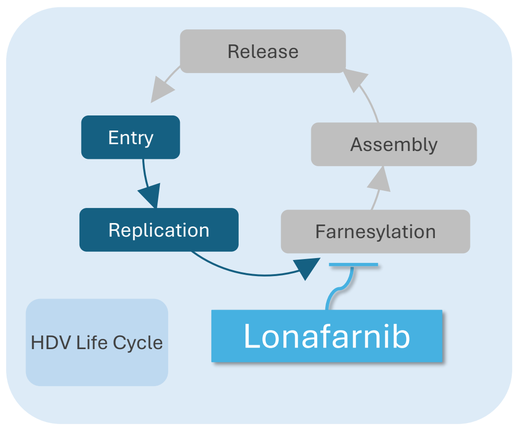
O. Etzion1, S. Hamid2, T. Asselah3, G. Gherlan4, M. Buti Feret5, P. Lampertico6, A. Turcanu7, H. Bonkovsky8, J. Lewis9, J. Ahmad10, S. Aleman11, J. Feld12, R. Taylor13, J. Sirois14, A. Hirani13, H. Agha13, L. Kawas13, N. Reau15, C. Koh16, T. Heller16, C. Yurdaydin17, X. Hua13, J. Glenn13,18

1. Soroka University Medical Center, Beersheba, Israel, 2. Aga Khan University, Karachi, Pakistan, 3. Hôpital Beaujon, APHP, Clichy and the University of Paris, Paris France, 4. Carol Davila University of Medicine and Pharmacy/Dr. Victor Babes Foundation, Bucharest, Romania, 5. Hospital Universitari Vall d'Hebron, Barcelona, Spain, 6. Fondazione IRCCS CA' Granda Ospedale Maggiore Policlinico, Milan, Italy, 7. The State University of Medicine and Pharmacy " N.Testemitanu", Republic of Moldova, 8. Wake Forest University School of Medicine, Winston-Salem NC, USA, 9. Medstar Georgetown University Hospital, Washington DC, USA, 10. Icahn School of Medicine at Mount Sinai, New York NY, USA, 11. Karolinska Universitetssjukhuset, Huddinge, Sweden, 12. University Health Network, Toronto, Canada, 13. EIT Pharma, Inc., Kirkland, WA, USA, 14. YBR Analytics, Jacksonville, USA, 15. Rush University Medical Center, Chicago IL, USA, 16. Liver Disease Branch, NIDDK, NIH, Bethesda MD, USA, 17. Koc University School of Medicine, Istanbul, Turkey, 18. Stanford University School of Medicine, Palo Alto CA, USA

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Introduction

Alanine aminotransferase (ALT) elevations have been reported following treatment discontinuation of currently-available chronic hepatitis D virus (HDV) and hepatitis B (HBV) treatments, but their clinical significance remains uncertain.



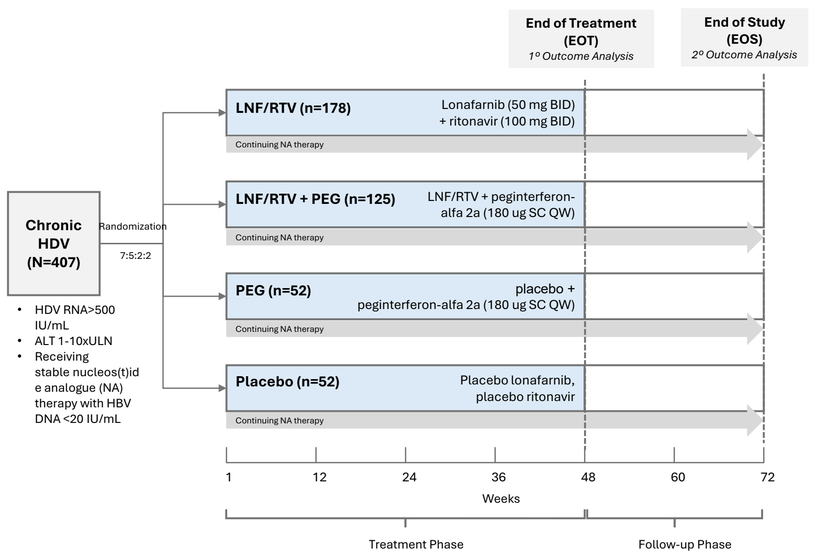
Lonafarnib (LNF), an oral host-targeting farnesyltransferase inhibitor being advanced as a 48-week treatment regimen for the treatment of HDV, has been associated with transient ALT elevations following treatment cessation.

Transient elevations in ALT are a feature of both disease progression and treatment in viral hepatitis.

Here we characterize the transient ALT elevations observed in D-LIVR, with a particular emphasis on safety and efficacy outcomes associated with these events.

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

- ALT elevation definitions were prespecified according to severity:
  - an ALT measurement > 2 X nadir and **> 10 X ULN**
  - an ALT measurement > 2 X baseline or **> 3 X ULN**
- The clinical significance of post-treatment ALT elevations was evaluated based on frameworks developed for evaluation of suppressive HBV therapies.
  - Viral reactivation associated with ALT elevation increases the risk of liver failure[1]
  - ALT elevations associated with reactivation of HBV infection are characterized by increased HBV DNA within months of nucleos(t)ide cessation[2]
  - ALT elevations can be categorized as "host-dominating" (aka beneficial) or "virus dominating" (aka detrimental) based on viral loads associated with the ALT elevation[3]

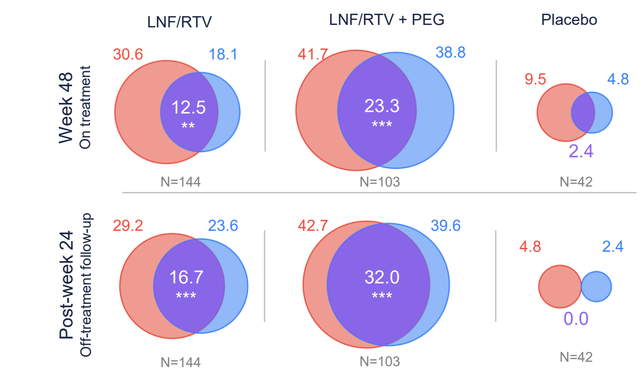
Results

PRIMARY AND COMPONENT EFFICACY

Both LNF-containing regimens met the primary composite efficacy endpoint compared to placebo at the end of treatment (EOT).

Efficacy measures were greater in combination with PEG and continued to develop during a 24-week off-treatment follow-up (EOS).

Figure 1 Primary composite and component efficacy at EOT and EOS



*** 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.
Per protocol analysis includes the completer population (all participants with a Week 48 visit) and EOS status determined using simplified LOCF imputation using PW20 data if PW24 data is missing.

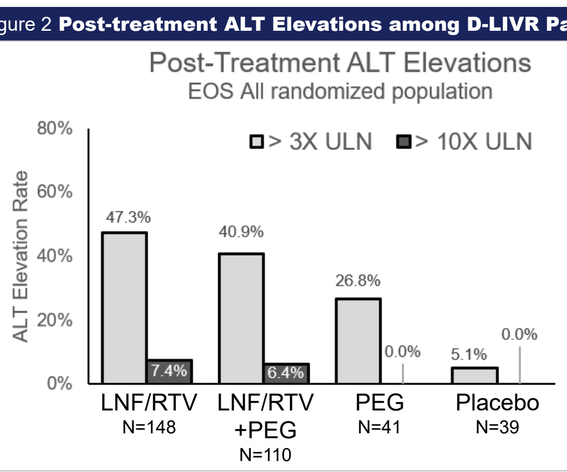
Post-Treatment ALT Elevations

POST-TREATMENT ALT ELEVATION RATES

Many LNF-treated patients experienced transient post-treatment elevations of ALT, and these events were most common in LNF/RTV monotherapy treatment arm (Figure 2).

No post-treatment ALT elevations were associated with concurrent INR > 2 X ULN or bilirubin > 2.5 X ULN, and there no cases of hepatic decompensation occurred during the study.

Figure 2 Post-treatment ALT Elevations among D-LIVR Participants



Posttreatment ALT flare is defined as an ALT measurement > 2 × reference or > 3 × ULN (grey) or >10 × ULN (black) 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.

ALT ELEVATIONS PRECEDE HDV RNA DECLINE

ALT elevations of > 10 X ULN were associated with subsequent HDV RNA decline over the subsequent 12 weeks, typical of host-dominating elevations[2,3](Table 1).

No ALT elevation of >10 X ULN was followed by a rise in HDV RNA of greater than 1 $\log_{10}$ IU/mL, as would be expected in virus-dominating elevations.

Table 1 HDV RNA dynamics following transient ALT elevations

	HDV RNA change after ALT elevation (patient counts)	LNF/RTV (N=148)	LNF/RTV + PEG (N=110)	PEG (N=41)
"Host-dominating"	>2 log decline	10	3	0
	1 to 2 log decline	5	3	0
	0 to 1 log decline	5	1	2
	0 to 1 log rise	1	2	0
"Virus-dominating"	1 to 2 log rise	0	0	0
	>2 log rise	0	0	0

Flares 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.

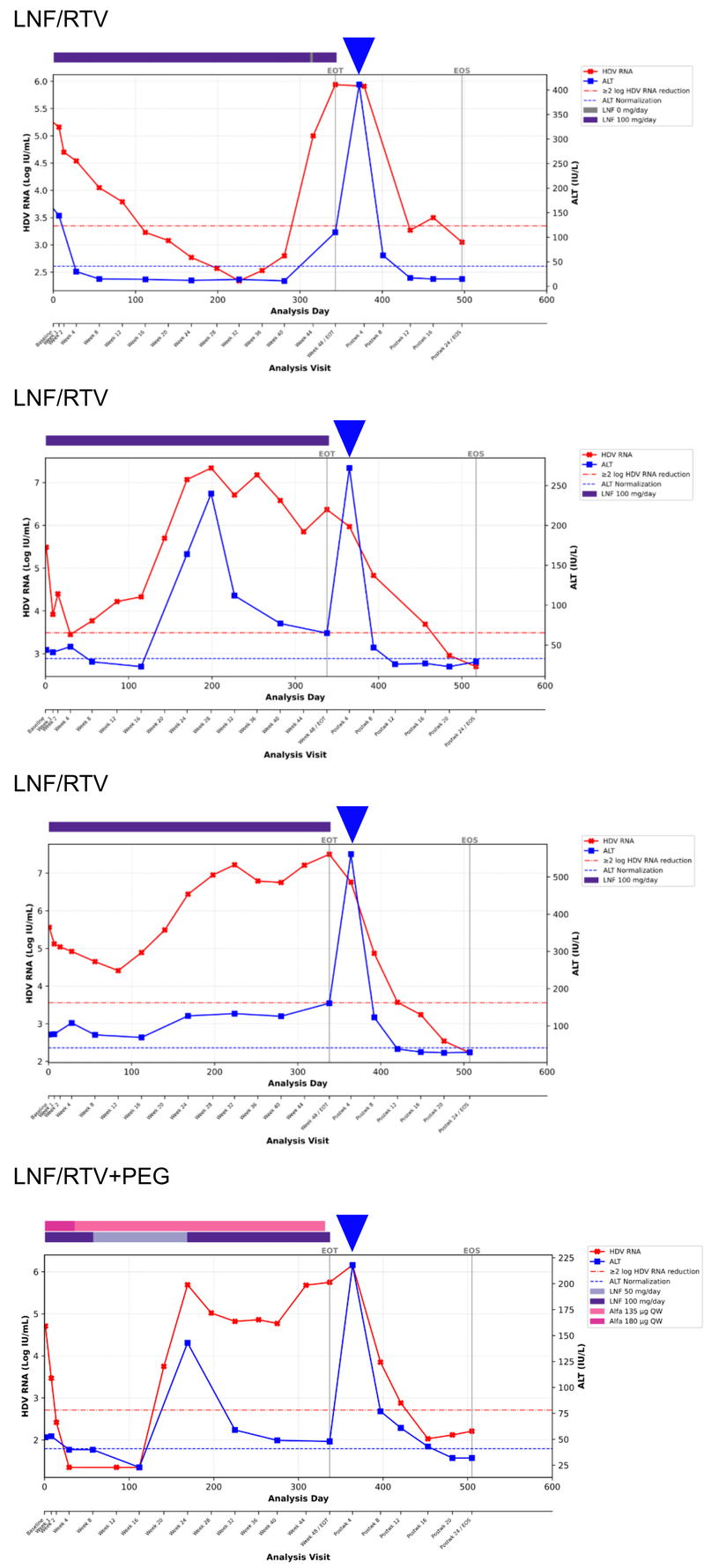
Representative Patient Profiles

ALT ELEVATION DYNAMICS AND SUBSEQUENT HDV RNA DECLINES

Representativve patient profiles (Figure 3) demonstrate the reduction in HDV RNA (red traces) in response to transient post-treatment ALT elevations (blue arrowheads, blue traces).

All patients represented were not composite responders at the end of treatment (EOT) but became composite responders at the end of follow-up (EOS).

Figure 3 Individual patient profiles representing HDV RNA dynamics following transient ALT elevations



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.

Conclusions

- Post-treatment ALT elevations following lonafarnib-based treatment cessation were generally:
  - Transient
  - Infrequently severe
  - Not associated with evidence of clinically significant liver injury or hepatic decompensation
- Post-treatment ALT elevations were frequently followed by decline in HDV RNA, suggesting a favorable host response rather than treatment-related hepatotoxicity, a view supported by independent hepatic adjudication committee review.
- Analysis of post-treatment ALT dynamics in response to LNF, the only late-stage oral agent under development for the treatment of HDV, indicates that treatment cessation is safe, and post-treatment immune engagement may support development of treatment effects off-treatment.

References

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2. Ghany, M. et al. (2020) Serum alanine aminotrasferased flares in chronic hepatitis B infection: the good and the bad. *Lancet Gastroenterology and Hepatology*. 4 (5) 406-417.
3. Liaw, Y. (2020) Hepatitis B flare after cessation of nucleos(t)ide analog therapy in HBeAg-negative chronic hepatitis B: To retreat or not to retreat. *Hepatology*. 73 (2) 843-852.

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.