Lonafarnib/ritonavir with or without peginterferon achieves rapid, durable responses in a chronic hepatitis D: extended analyses from the phase 3 D-LIVR trial

Robert Taylor[1], Ohad Etzion[2], Saeed Sadiq Hamid[3], Tarik Asselah[4, 5], George Sebastian Gherlan[6], Maria Buti[7], Pietro Lampertico[8], Adela Turcanu[9], Tsarynna Petrivna[10], Liana Gheorghe[11], George Stancu[11], Natalia Voronkova[12], Natalia Barsukova[13], Soo Aleman[14], Jordan J. Feld[15], Jean-Karl Sirois[16], Armaan Hirani[1], Hebaalla Agha[1], Leen Kawas[1], Nancy S. Reau[17], Christopher Koh[18], Theo Heller[18], Cihan Yurdaydin[19] , Xue Hua[1], Jeffrey Glenn[1, 20]

Key Messages

- **Lonafarnib/ritonavir (LNF/RTV) is the first and only oral therapy** in late-stage development for chronic hepatitis D, with a unique virion-assembly disruption mechanism.
- **LNF-based regimens met the Phase 3 D-LIVR primary endpoint**, demonstrating significant composite, virologic, and biochemical benefit versus placebo.
- **Responses were durable** 24 weeks after treatment cessation, supporting sustained therapeutic impact.
- LNF-based therapies promote composite, virologic, and biochemical treatment response **faster than peginterferon alfa-2a monotherapy**.
- LNF/RTV provides a potential backbone for future combination regimens due to its oral administration, unique MOA, and favorable safety profile.

EASL CONGRESS
Barcelona Spain 2026
27–30 May

Author Affiliations

1 EIT Pharma, Inc., Kirkland, United States, 2 Soroka, University Medical Center, Be'er Sheva, Israel, 3 Aga Khan University, Karachi, Pakistan, 4 Hopital Beaujon, University of Paris, Clichy, France, 5 University of Paris, Paris, France, 6 Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, 7 Hospital Universitari Vall d'Hebron, Barcelona, Spain, 8 Fondazione IRCCS CA' Granda Ospedale Maggiore Policlinico, Milan, Italy, 9 The State University of Medicine and Pharmacy, Chisinau, Moldova, 10 International Institute of Clinical Research, Kyiv, Ukraine, 11 Institutul Clinic Fundeni, Bucharest, Romania, 12 H-Clinic, Moscow, Russian Federation, 13 Center for Targeted Therapy, LLC., Moscow, Russian Federation, 14 Korolinska Universitetssjukheset, Huddinge, Sweden, 15 University Health Network, Toronto, Canada, 16 YBR Analytics, Toronto, Canada, 17 Rush University Medical Center, Chicago, United States, 18 Liver Disease Branch, NIDDK, NIH, Bethesda, United States, 19 Koc University School of Medicine, Istanbul, Türkiye, 20 Stanford University School of Medicine, Palo Alto, United States

References

Bordier BB, Ohkanda J, Liu P, et al. In vivo antiviral efficacy of prenylation inhibitors against hepatitis delta virus. *Journal of Clinical Investigation*. 2003;112(3):407–414.

Glenn, J. S., Watson, J. A., Havel, C. M., et al. (1992). Identification of a prenylation site in delta virus large antigen. Science, 256(5061), 1331–1333.

Lampertico, P., Bogomolov, P. O., & Chulanov, V. (2025). Phase 2 randomised study of bulevirtide as monotherapy or combined with peg-IFNα-2a as treatment for chronic hepatitis delta. Liver International, 45, e70008.

Otto, J. C., & Casey, P. J. (1996). The hepatitis delta virus large antigen is farnesylated both in vitro and in animal cells. *Journal of Biological Chemistry*, *271*(9), 4569–4572.

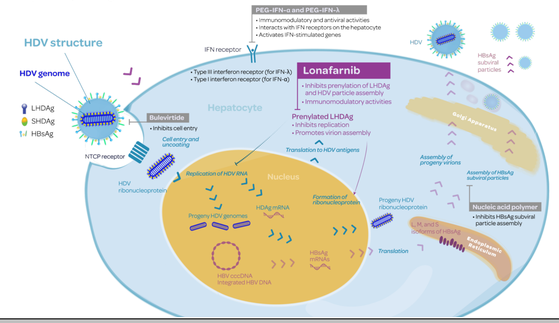
Sato, S., Cornillez-Ty, C., & Lazinski, D. W. (2004). By inhibiting replication, the large hepatitis delta antigen can indirectly regulate amber/W editing and its own expression. *Journal of Virology*, *78*(15), 8120–8134.

Hammerich, L., Tacke, F. Hepatic inflammatory responses in liver fibrosis. Nat Rev Gastroenterol Hepatol 20, 633–646 (2023). https://doi.org/10.1038/s41575-023-00807-x

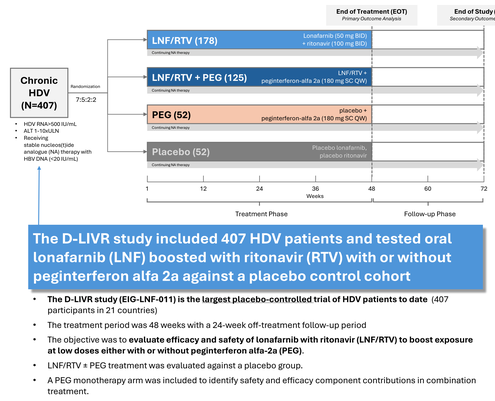
BACKGROUND

Lonafarnib (LNF) is an oral small molecule farnesyltransferase (FT) inhibitor that acts inside hepatocytes to inhibit assembly and secretion of infective hepatitis delta virus (HDV) particles

- **LNF is the only late-stage oral therapeutic under development for the treatment of chronic HDV infection. It is stable at room temperature, offering an accessible treatment option for patients.**
- By inhibiting FT within infected hepatocytes, LNF prevents farnesylation of the L-HDAg, a post-translational modification required for HDV virion assembly and secretion (Glenn et al., 1992; Otto and Casey, 1996; Bordier et al., 2003).
- Intracellular accumulation of immature HDV particles is expected to enhance innate immune sensing; in preclinical studies, post-infection treatment with LNF resulted in marked induction of interferons and interferon-stimulated genes (ISGs), with increases ranging from 11- to 39-fold (Sato et al, 2004; Lempp et al, 2019).



STUDY METHOD



The D-LIVR study included 407 HDV patients and tested oral lonafarnib (LNF) boosted with ritonavir (RTV) with or without peginterferon alfa 2a against a placebo control cohort

- **The D-LIVR study (EIG-LNF-011) is the largest placebo-controlled trial of HDV patients to date** (407 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.

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

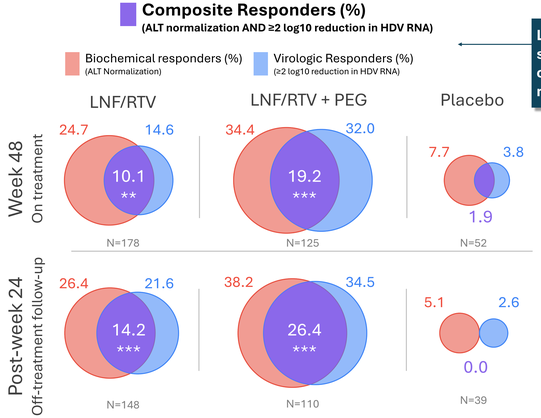
- **26.5% of the population had cirrhosis** at baseline
- **All study participants received nucleos(t)ide analog therapy** throughout the study to manage HBV coinfection

Characteristic	LNF/RTV n=178	LNF/RTV+PEG n=125	PEG n=52	Placebo n=52	Overall 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)	0 (0.0)	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 (13063.9)	9421.6 (8156.8)	11683.5 (12161.3)	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 (822.9)

RESULTS: Efficacy

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

Lonafarnib treatment achieves significant composite response and component virologic and biochemical responses



*** 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-based treatments demonstrated **statistically significant improvements in the primary composite efficacy endpoint** compared with placebo following a 48-week treatment course and after a 24-week follow-up (Purple overlap).
- This endpoint captures concurrent virologic suppression and biochemical improvement and is recognized by the FDA as a surrogate reasonably likely to predict clinical benefit in support of accelerated approval.
- **Both the virologic response (≥2 log_{10} decline in HDV RNA [Blue]) and biochemical response (ALT normalization [Red]) demonstrated statistically significant improvements versus placebo** for LNF/RTV and LNF/RTV + PEG, with each comparison achieving significance independently.
- The proportion of randomized patients achieving the primary composite response at Week 48 with oral LNF/RTV (18/178, 10.1%) was **comparable to that observed with weekly injectable PEG monotherapy** (5/52, 9.6%)

Durability

Treatment response to LNF therapy was durable over a 24-week off-treatment follow-up, and new responders emerged during follow-up

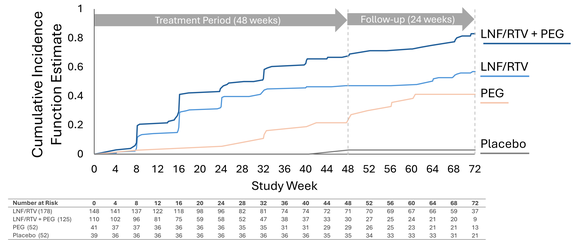
- **Durability of the composite** response was evaluated based on the proportion of subjects who achieved a composite response at EOT and maintained that response at EOS, 24 weeks post-treatment.
- **Newly emergent composite responses at 24 weeks post-treatment** were evaluated among subjects who did not achieve a composite response at EOT
- **On-treatment composite efficacy endpoint at Week 48 is predictive of post-treatment clinical benefit**, and development of composite response among non-responders was also observed

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)

EOS composite response was determined using the post hoc EOS-ITT analysis with a simplified last-observation-carried-forward (LOCF) approach and was defined as a ≥2 log_{10} decline in HDV RNA and ALT normalization at 24 weeks post-treatment relative to baseline.

Speed of Response

Speed of Response:
Cumulative Composite Responders by Treatment

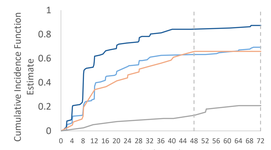


Number at Risk	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72
LNF/RTV (178)	148	141	137	122	118	98	96	82	81	74	74	72	71	70	69	67	66	59	37
LNF/RTV + PEG (125)	110	102	96	81	75	59	58	52	47	38	37	33	30	27	25	24	21	20	9
PEG (52)	41	37	37	36	36	36	36	35	35	31	31	29	29	26	25	23	21	21	13
Placebo (52)	39	36	36	36	36	36	36	36	36	36	35	35	34	33	33	33	31	31	21

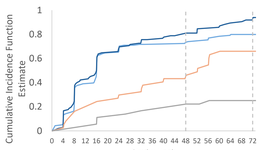
LNF-based treatments produce rapid treatment response in composite, virologic, and biochemical endpoints

- In post-hoc analysis, **the rate of achievement of treatment response** was evaluated as a clinically relevant descriptive measure.
- **This visualization represents the cumulative incidence of response**, that is the time-to-achieving response for the first time, at which point the response may or may not remain. **It is not intended to demonstrate a sustained response.**
- Time-to-response is a key consideration in the management of chronic HDV, **as early disease control may reduce disease burden and mitigate ongoing liver injury** (Hammerich and Tacke, 2023).
- Speed of response is also a key consideration for components of potential combination therapies.
- **LNF therapy with or without PEG produces composite treatment response more rapidly than PEG monotherapy.**
- Combination therapy produces virologic response (≥2 log HDV RNA reduction) more rapidly than either LNF/RTV or PEG monotherapy.
- LNF/RTV either with or without PEG produces rapid ALT normalization.

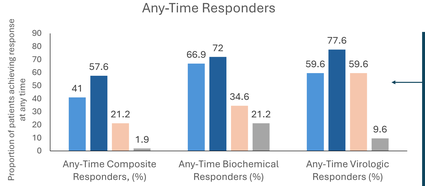
Cumulative Virologic Response



Cumulative ALT Normalization



Any-Time Responders



Most patients treated with LNF/RTV + PEG achieved composite treatment response at some point during the trial

- In a post hoc time-to-response analysis, **the first occurrence at which patients met the prespecified composite, virologic, and biochemical response criteria was evaluated,** with such patients classified as "any-time responders" presented as a crude proportion of the all randomized population.
- This analysis applied the same responder definitions as the primary analysis but **extended the evaluation window beyond the single assessment at Week 48** or end of treatment.
- This descriptive analysis demonstrated a broader response profile across composite, virologic, and biochemical endpoints.

CONCLUSIONS

- Lonafarnib (LNF) is a small molecule farnesyltransferase inhibitor that prevents assembly and secretion of infective HDV particles, and is the only oral HDV treatment in late-stage clinical development.
- LNF, delivered with pharmacokinetic booster ritonavir (RTV) either with or without peginterferon alfa-2A (PEG) was tested in D-LIVR, the largest placebo-controlled interventional trial in HDV patients.
- The primary endpoint of the D-LIVR trial was achieved, with statistically significant improvement in composite virologic and biochemical endpoints at Week 48 on treatment.
- The treatment benefit was durable after a 24-week off-treatment follow-up period and new treatment responders emerged during the follow-up.
- LNF-based treatment regimens produced composite, virologic, and biochemical improvements more rapidly and in a broader group of patients at any time compared to standard of care, PEG monotherapy.

Future Directions

- A trial will assess long-term clinical benefit of a 48-week treatment regimen of LNF/RTV ± PEG is being initiated
- Combination studies with LNF to improve the management of HDV and long-term outcomes should be considered