Week 72 Results of the Phase 3 *D-LIVR* Study: a Randomized Double-Blind, Placebo-Controlled Trial, Evaluating the Safety and Efficacy of Lonafarnib-Boosted with Ritonavir with or without Peginterferon Alfa in Patients with Chronic Hepatitis Delta

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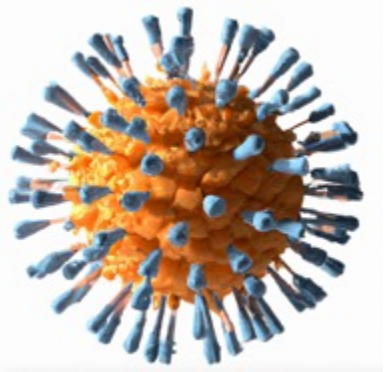
Background

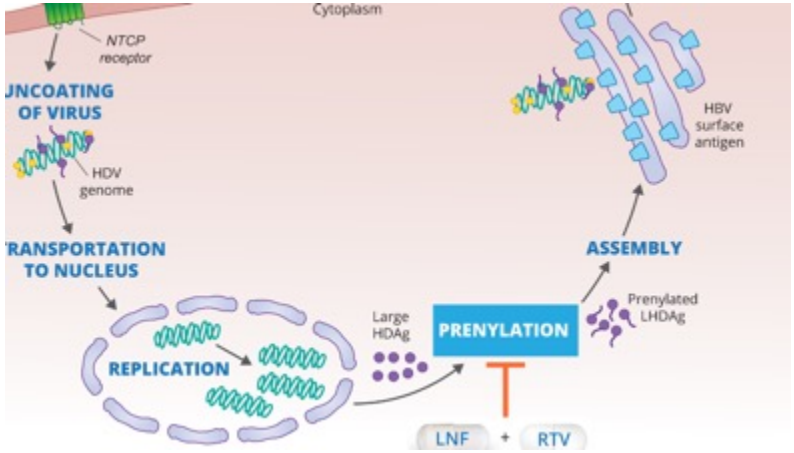


- HDV is a small satellite virus that depends on the surface antigen of HBV for host infection[1]
- Global prevalence of 10-20 million people[2]
- Rapid progression to cirrhosis and a higher rate of ESLD complications, HCC, and death compared to HBV mono-infection[3]
- No FDA-approved therapy; single drug in the process of FMA (EMA)
- Treatment for HDV presents an urgent unmet medical need

[1]Yardeni D, et al. Chronic hepatitis D-What is changing? J Viral Hepat. 2022 Apr;29(4):240-251..[2]Stockdale AJ et al. The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. J Hepatol. 2020 Sep;73(3):523-532. [3]Romeo R et al. A 28-year study of the course of hepatitis delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. *Gastroenterology*. 2009; **136**: 1629- 1638.

Lonafarnib

- First-in-class prenylation inhibitor[1]
- LNF disrupts virus assembly by inhibiting the prenylation of LHDAg and its binding to HBsAg
- LNF showed suppression of HDV levels in a proof-of-concept study[2]
- Improved efficacy and tolerability of LNF boosted with RTV and in combination with pegIFN Alfa for 24 weeks[3-4]



[1]Glenn JS et al. Identification of a prenylation site in delta virus large antigen. Science. 1992 May 29;256(5061):1331-3. [2]Koh C et al. Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomized, double-blind, placebo-controlled phase 2A trial. [3]Yurdaydin C et al. Optimizing lonafarnib treatment for the management of chronic delta hepatitis: The LOWR HDV-1 study. Hepatology. 2018 Apr;67(4):1224-1236 [4]Yurdaydin C et al. A phase 2 dose-finding study of lonafarnib and ritonavir with or without interferon-alpha for chronic delta hepatitis. Hepatology. 2022 Jun;75(6):1551-1565.

D-LIVR Phase 3 Clinical trial

Objective

To evaluate the safety, tolerability, and efficacy of LNF boosted with RTV with or without pegIFN Alfa for treatment of chronic HDV infection compared to placebo

Primary Endpoint at Week 48

≥ 2 log decline in HDV RNA
+
Normalization of ALT

Secondary Endpoint at Week 48

No worsening in fibrosis
+
≥ 2-point in Ishak HAI Score

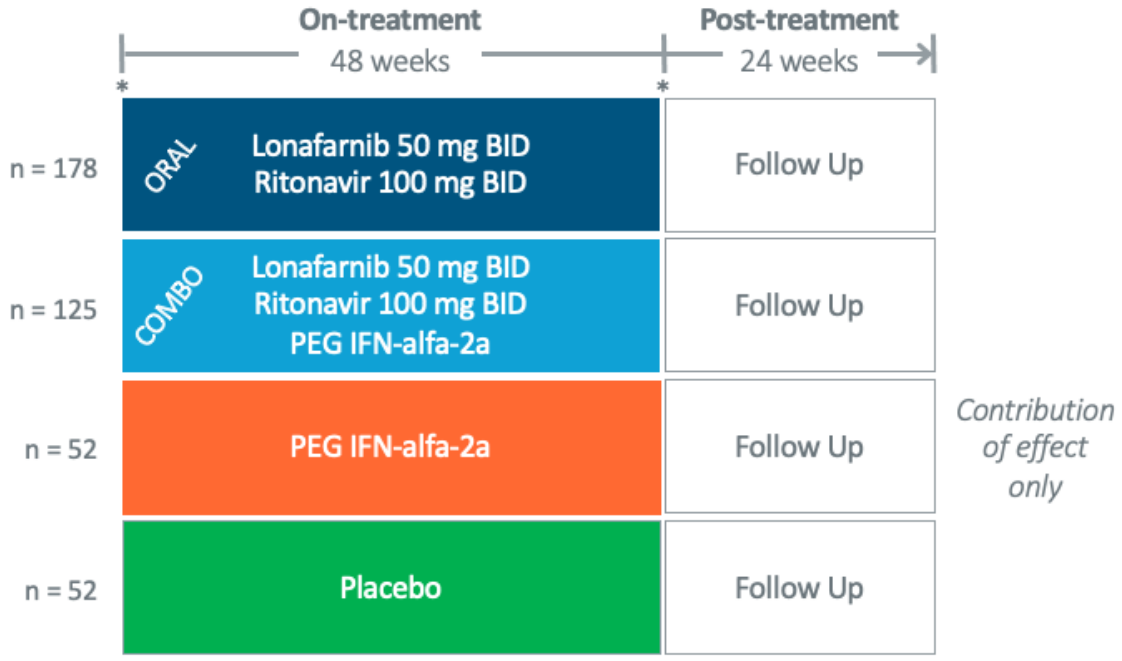
Key Inclusion criteria

CHD with compensated liver disease

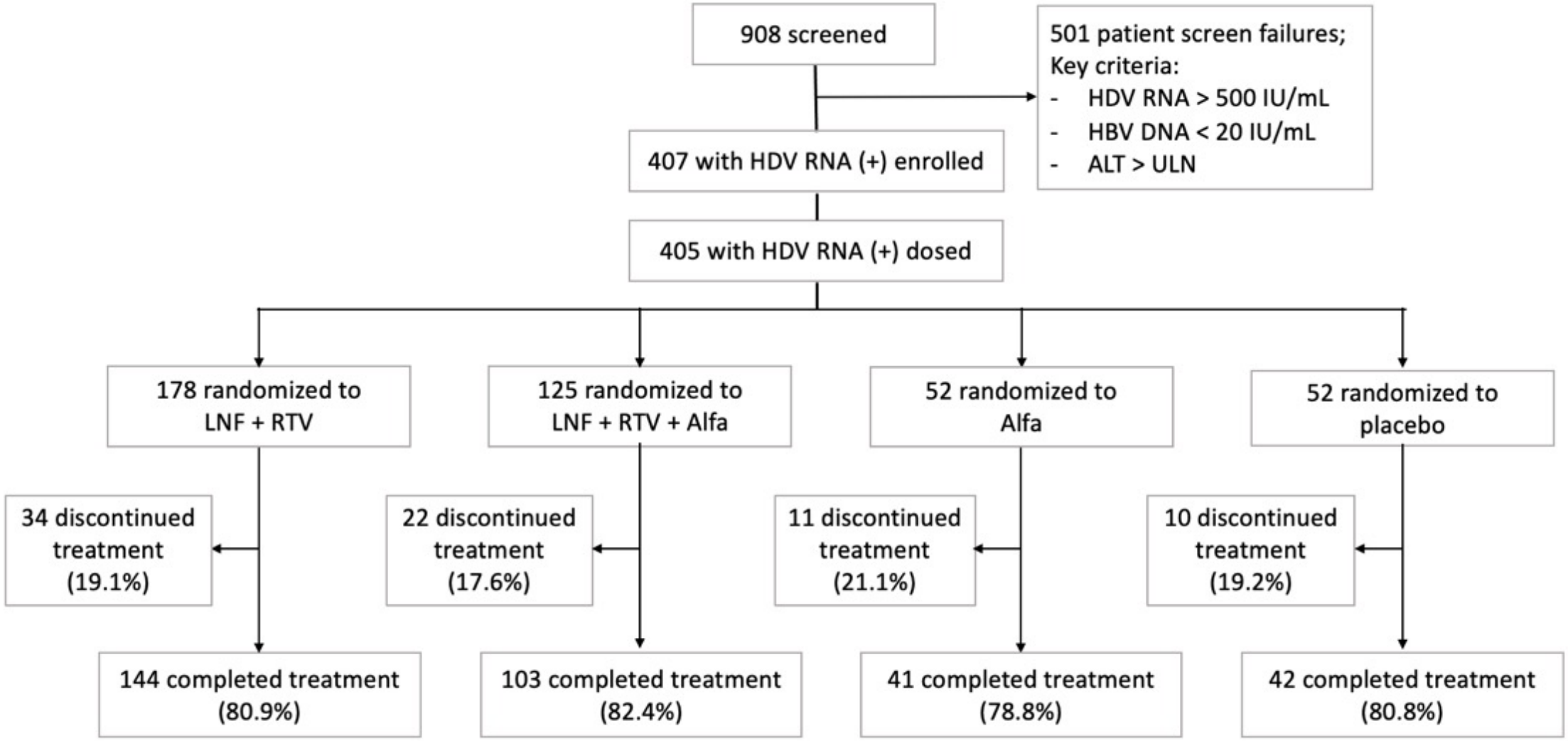
HDV RNA > 500 IU/mL

ALT > 1.3X < 10X ULN

HBV DNA < 20 IU/mL



D-LIVR: Patient Disposition

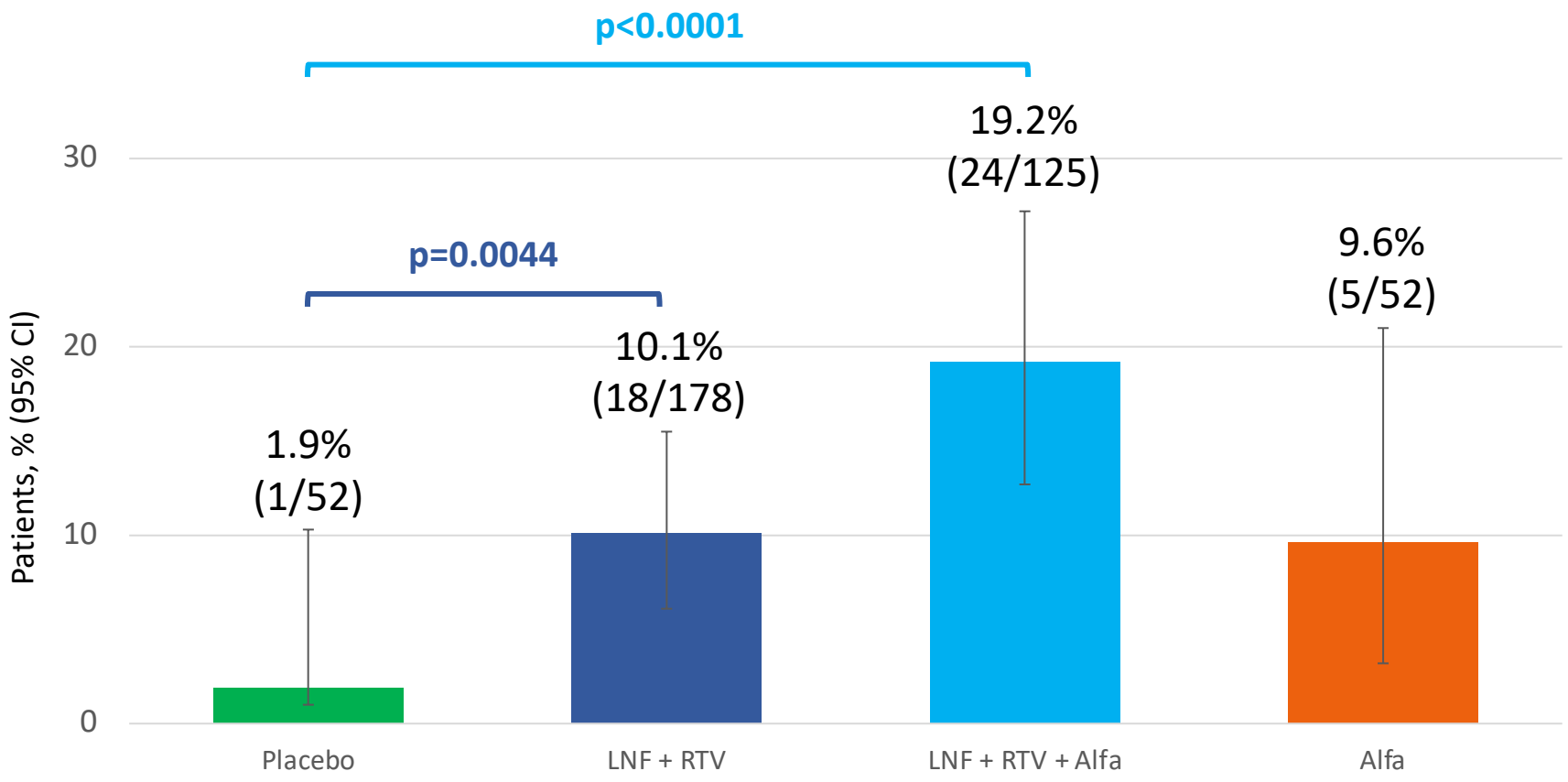


D-LIVR: Baseline Patient Characteristics

		Placebo (n=52)	LNF + RTV (n=178)	LNF + RTV + Alfa (n=125)	Alfa (n=52)	Total (N=407)
Mean age, y (SD)		45.7 (10.9)	42.9 (10.8)	41.4 (11.5)	42.3 (11.0)	42.7
Men, n (%)		39 (75)	126 (71)	84 (67)	33 (64)	282 (69)
Race, n (%)	White	42 (81)	130 (73)	85 (68)	41 (79)	298 (73)
	Asian	10 (19)	40 (23)	35 (28)	10 (19)	95 (23)
	Black	0	3 (2)	3 (2)	0	6 (2)
	Other/no reported	0	5 (3)	1 (1)	1 (2)	7 (2)
Region	Asia	6 (12)	25 (14)	21 (17)	7 (14)	59 (15)
	Europe	43 (83)	127 (71)	92 (74)	41 (79)	303 (74)
	North America	1 (2)	14 (8)	9 (7)	2 (4)	26 (6)
	Other	2 (4)	12 (7)	3 (2)	2 (4)	19 (5)
Mean ALT, U/L (SD)		122 (83)	100 (69)	99 (73)	82 (47)	100 (70)
Mean HDV RNA, log IU/mL (SD)		4.97 (1.12)	4.94 (1.13)	5.14 (1.17)	4.88 (1.19)	5.00 (1.15)
HDV genotype, n (%)	1	47 (90)	174 (98)	118 (94)	52 (100)	391 (96)
	4 / 5 / 8 / not reported	1 (2) / 0 / 0 / 4 (8)	0 / 1 (0.6) / 0 / 3 (2)	0 / 0 / 1 (1) / 6 (5)	0 / 0 / 0 / 0	16 (4)
Median HBsAg, log IU/mL (range)		3.92 (2.18, 4.75)	3.83 (2.11, 4.75)	3.91 (1.16, 4.75)	3.92 (2.22, 4.63)	4.00 (1.16, 4.75)
Cirrhosis, n (%)		15 (29)	47 (26)	32 (26)	14 (27)	108 (27)

Primary Endpoint: Composite Response at Week 48

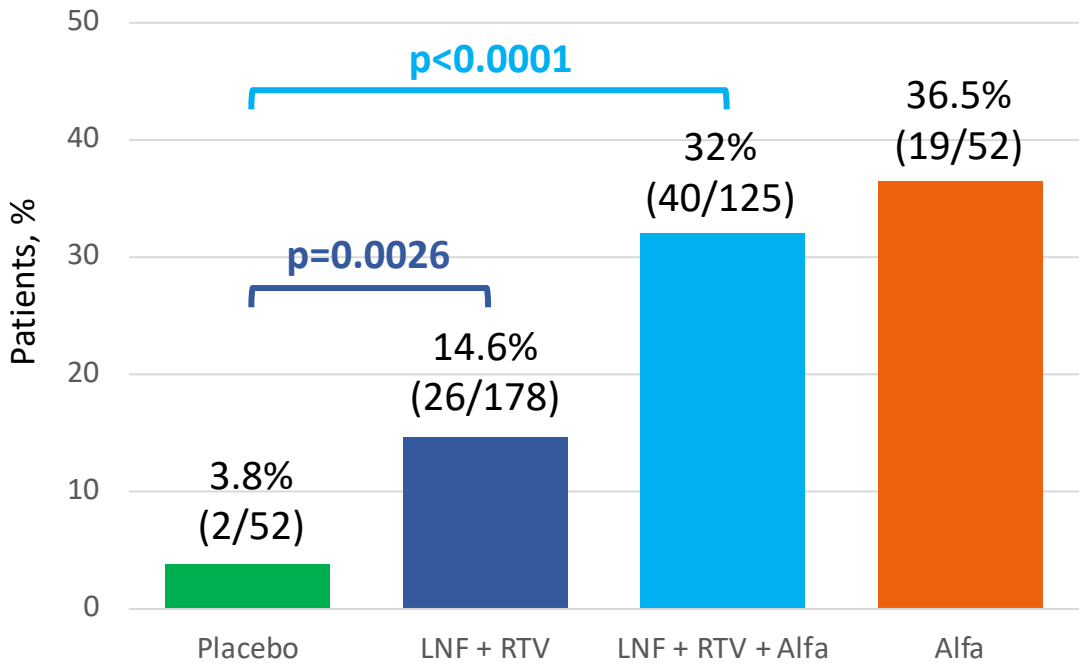
INTENT TO TREAT (ITT) POPULATION (N=405)



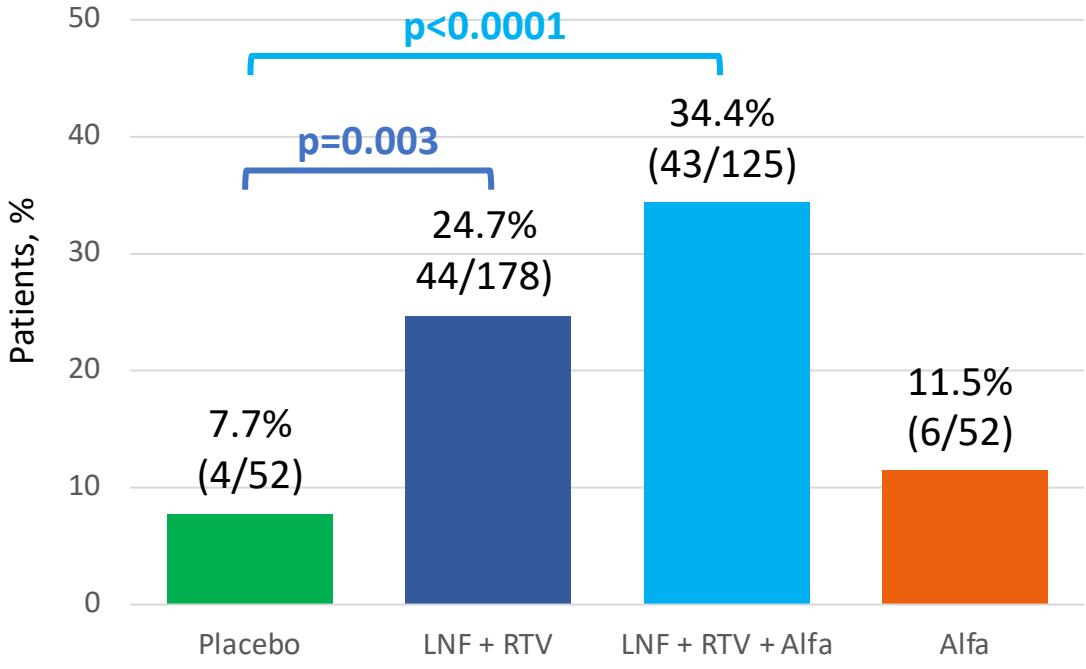
Key Secondary Endpoints: Virological and Biochemical Response at Week 48

INTENT TO TREAT (ITT) POPULATION (N=405)

Virological Response:
≥ 2 Log Decline in HDV RNA



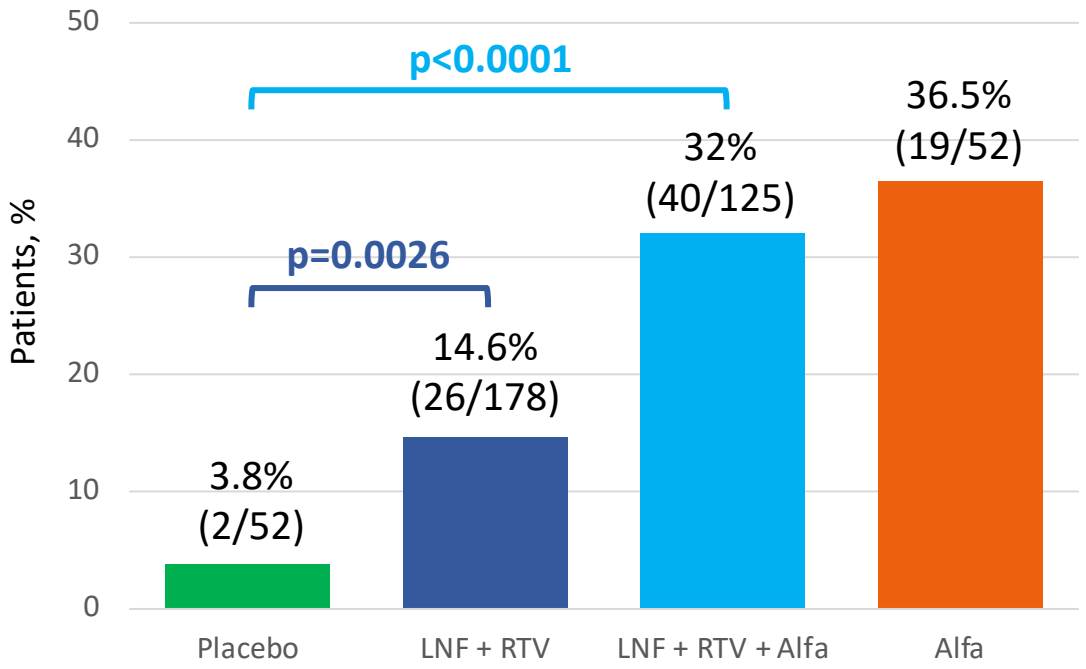
Biochemical Response:
ALT Normalization



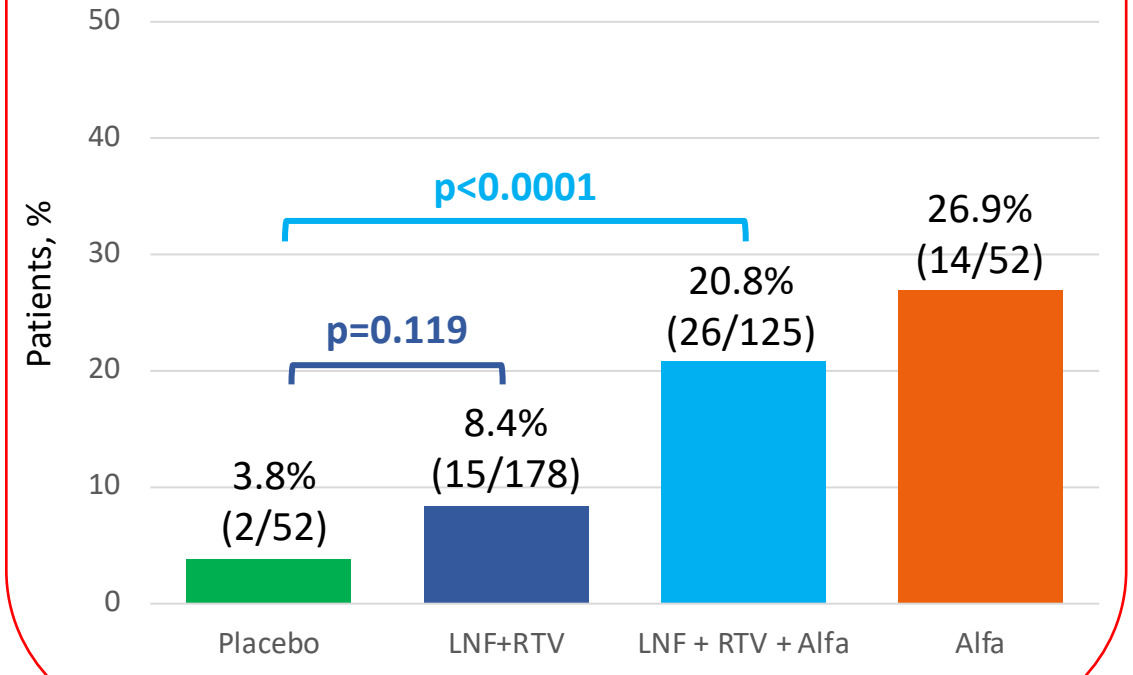
Key Secondary Endpoints:
% Patients Achieving HDV RNA < LLOQ at Week 48

INTENT TO TREAT (ITT) POPULATION (N=405)

Virological Response:
≥ 2 Log Decline in HDV RNA



Virological Response:
< LLOQ (TD OR TND) in HDV RNA

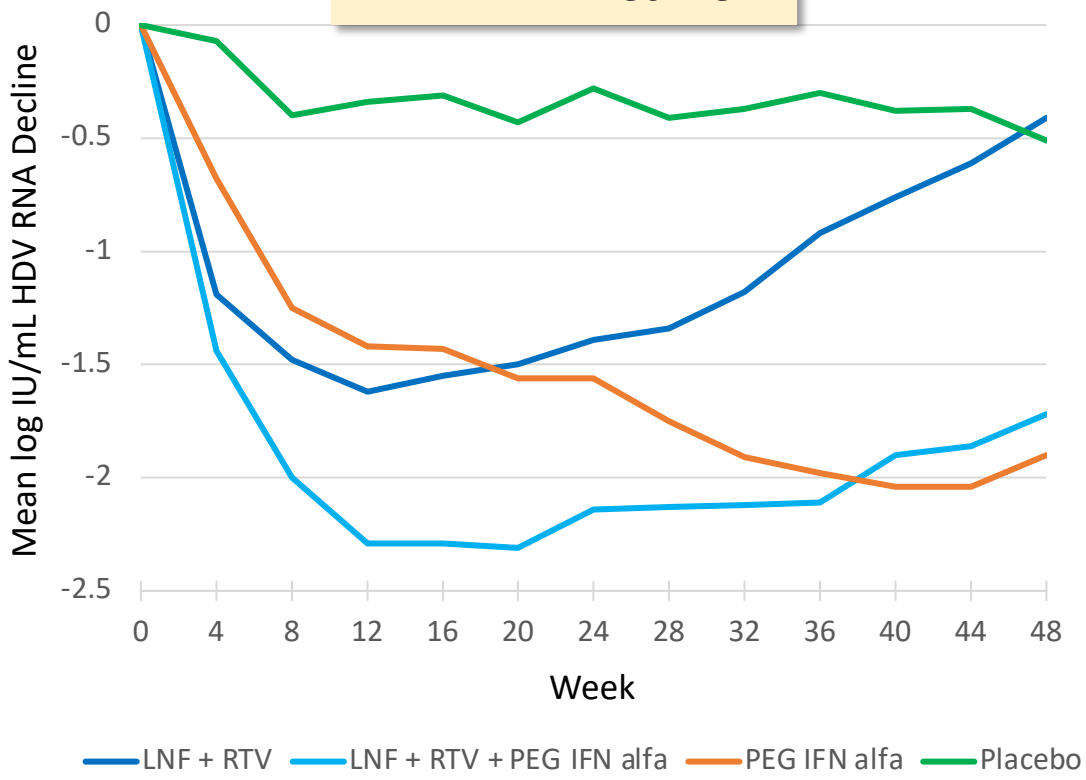


* Quest Diagnostics: Limit of quantification = 40 IU/mL

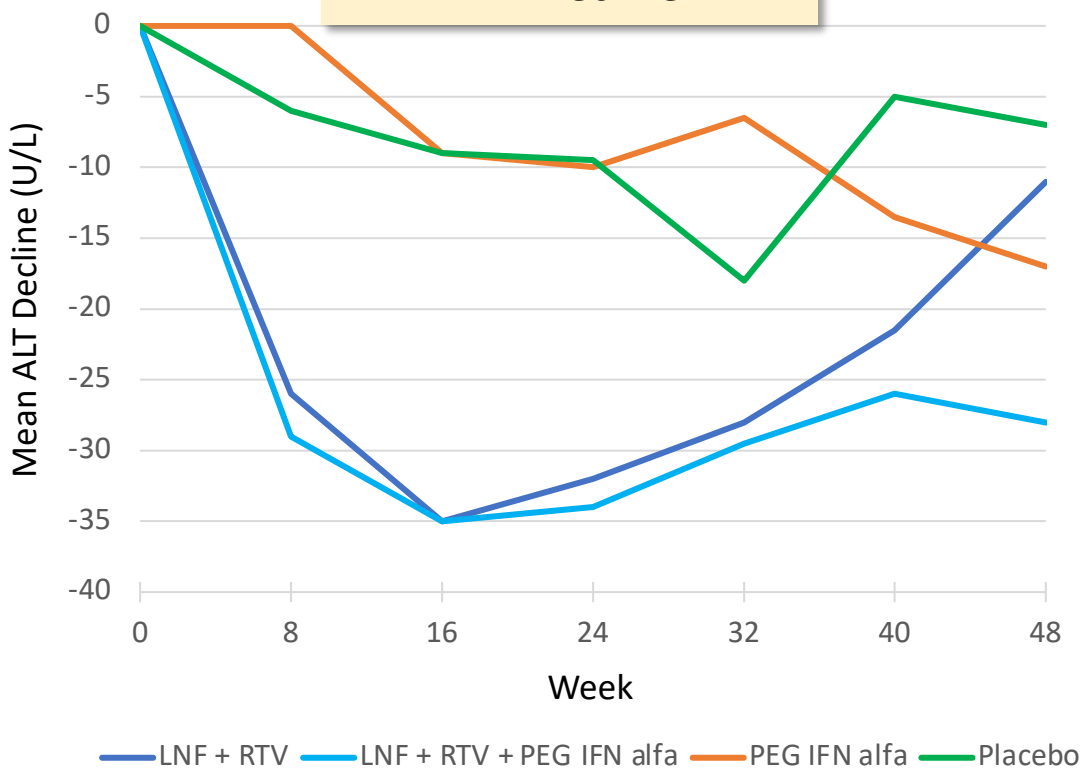
Mean HDV RNA and ALT Decline Through End of Treatment

INTENT TO TREAT (ITT) POPULATION (N=405)

Virological Response:
HDV RNA Decline



Biochemical Response:
ALT Decline



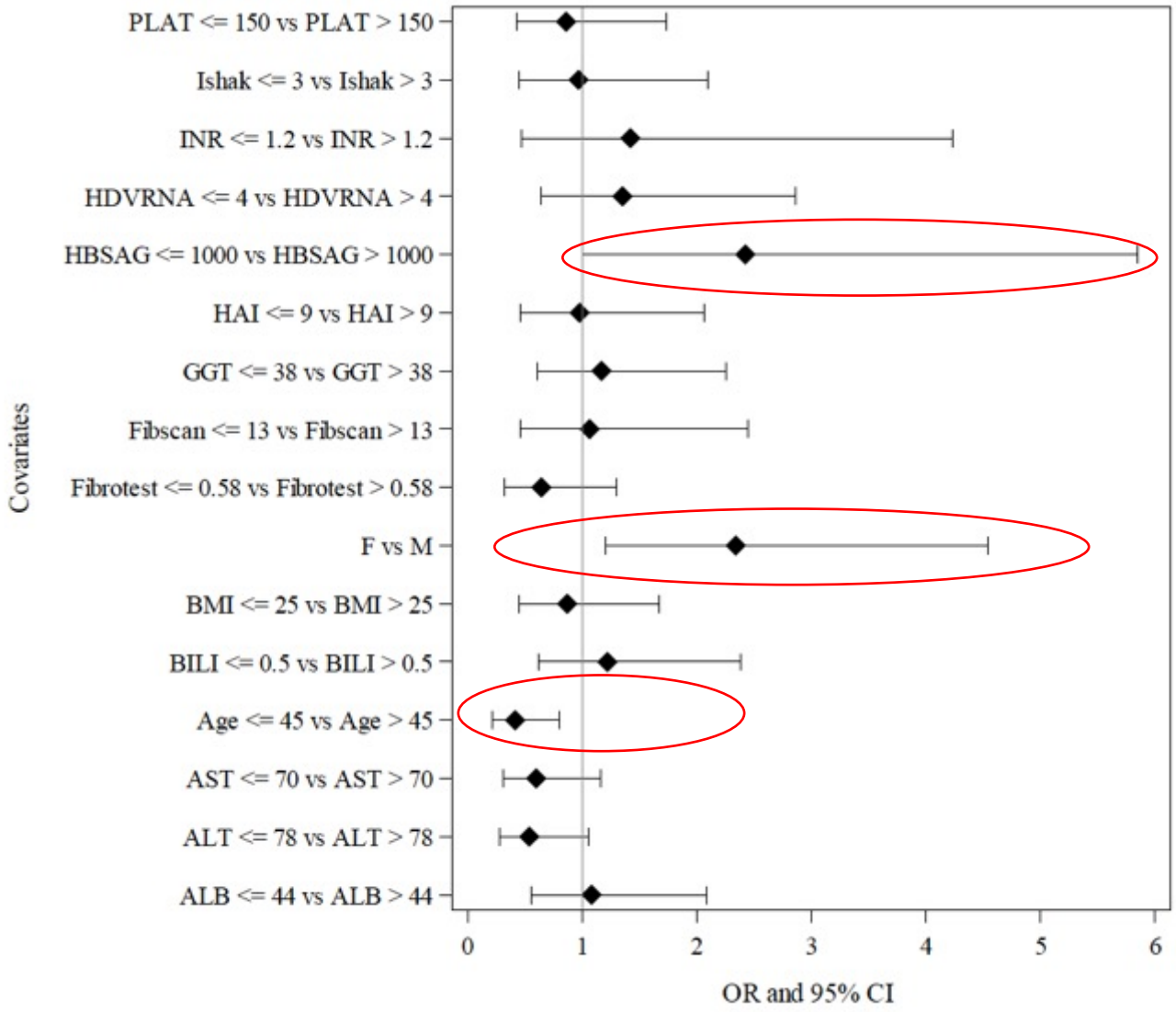
Key Secondary Endpoints: Histologic Response Rates at Week 48

EVALUABLE PAIRED LIVER BIOPSIES (N=229)

	% (n)			
Response	LNF + RTV n=107	LNF + RTV + Alfa n=66	Alfa n=26	Placebo n=30
Histologic Composite Endpoint* In Patients with Evaluable Paired Biopsies (n=229)	33% (35) (p=0.61)	53% (35) (p=0.0139)	38% (10) (p=0.46)	27% (8)

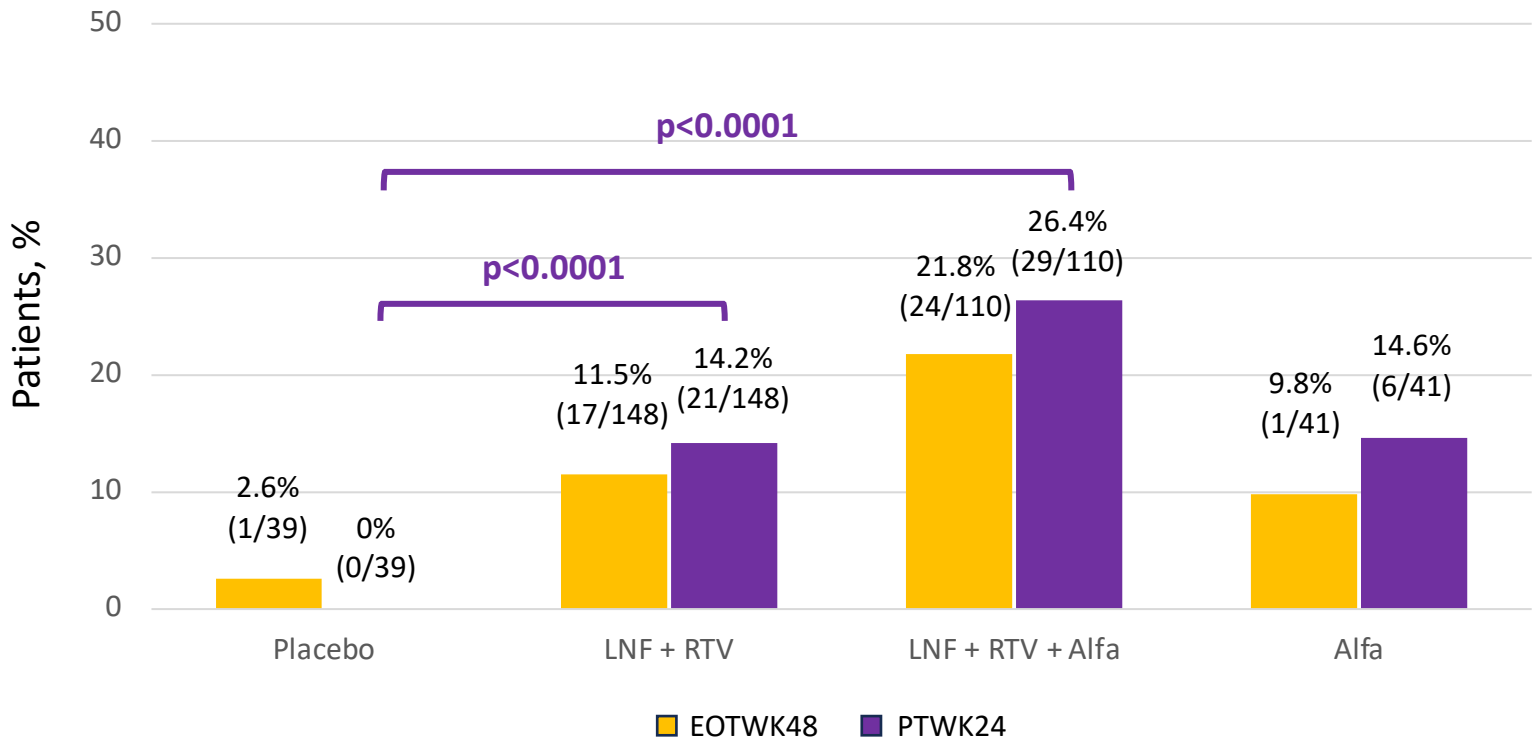
* ≥ 2-point improvement in histology activity index (HAI) score + no worsening in Ishak fibrosis score

Factors Associated with Composite Response at Week 48



End of Study Results: Composite Endpoint

RANDOMIZED POPULATION, N=338

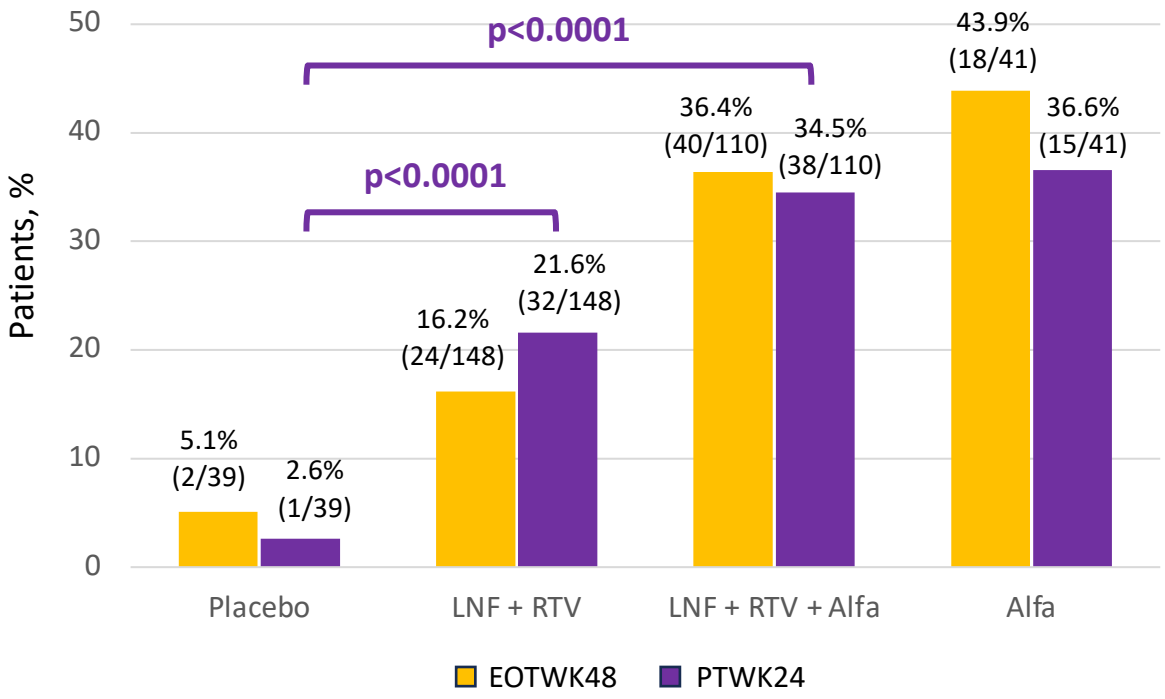


*PTWK24 responders may be different from responders at EOTWK48

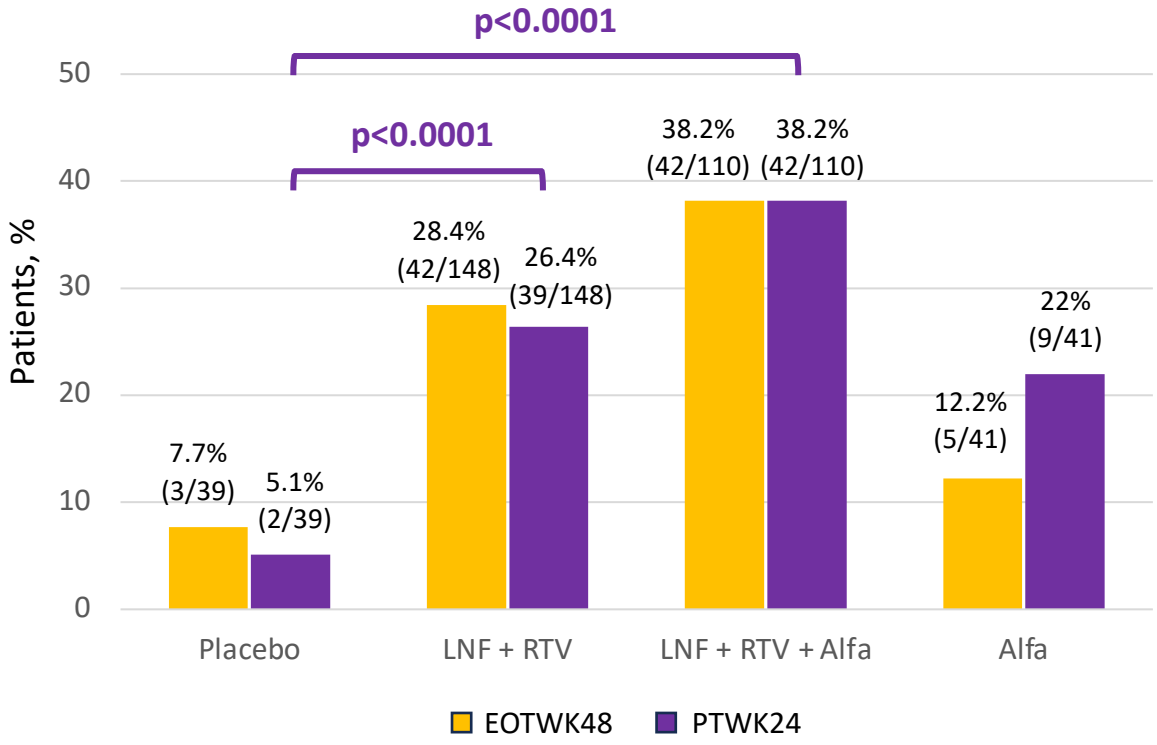
End of Study Results: Virological & Biochemical Components

RANDOMIZED POPULATION, N=338

≥2 Log HDV RNA



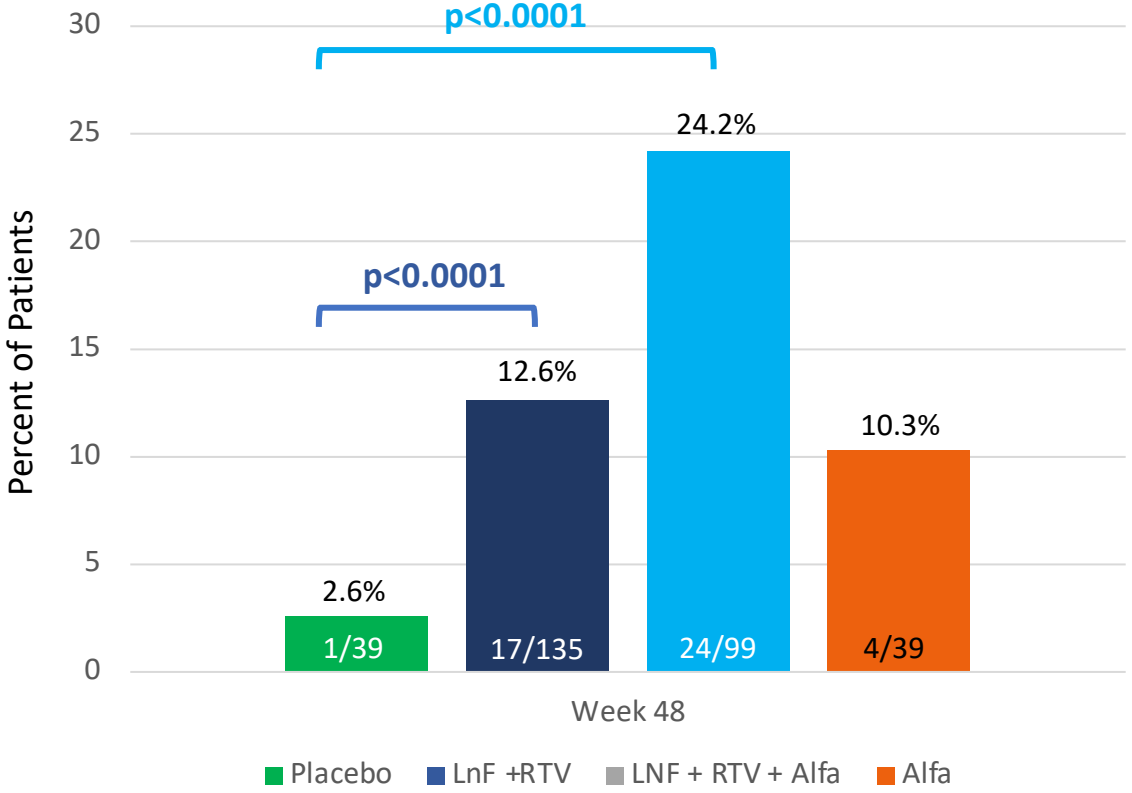
ALT Normalization

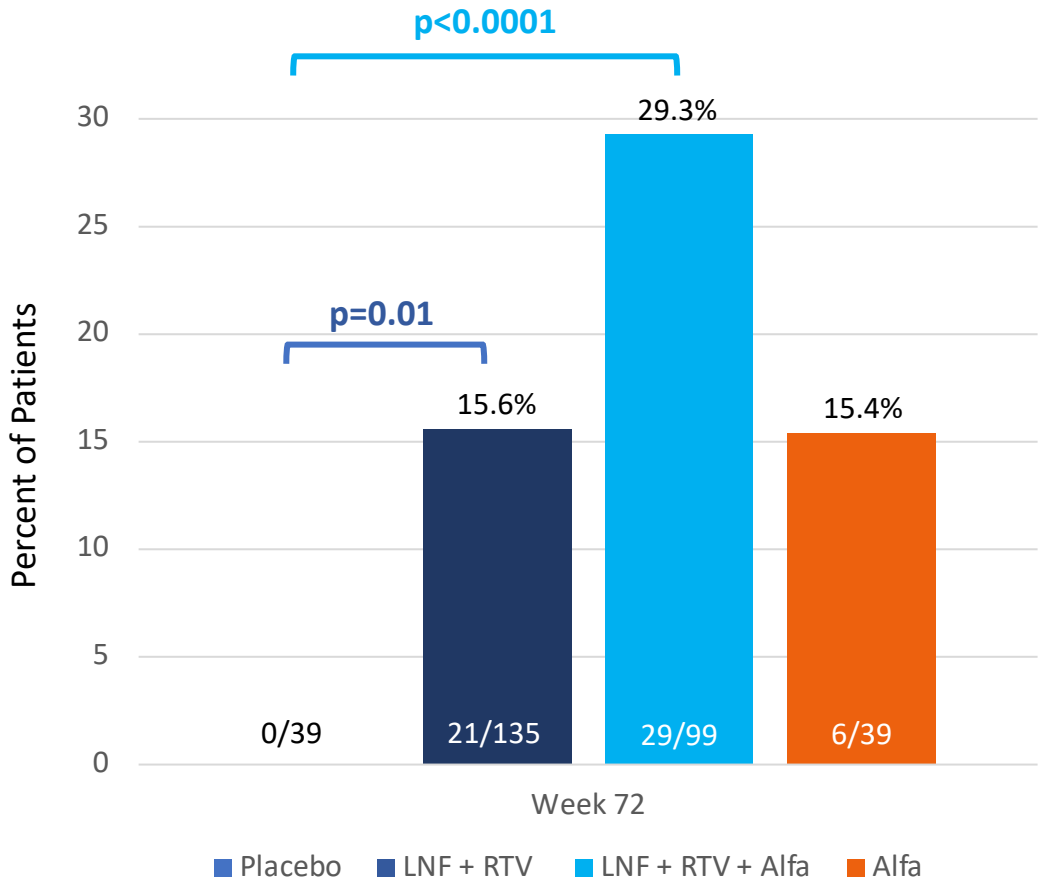


*PTWK24 responders may be different from responders at EOTWK48

Composite Endpoint Response through End of Follow-up

PATIENTS WHO COMPLETED TREATMENT AND FOLLOWED THROUGH WEEK 72 (N=312)

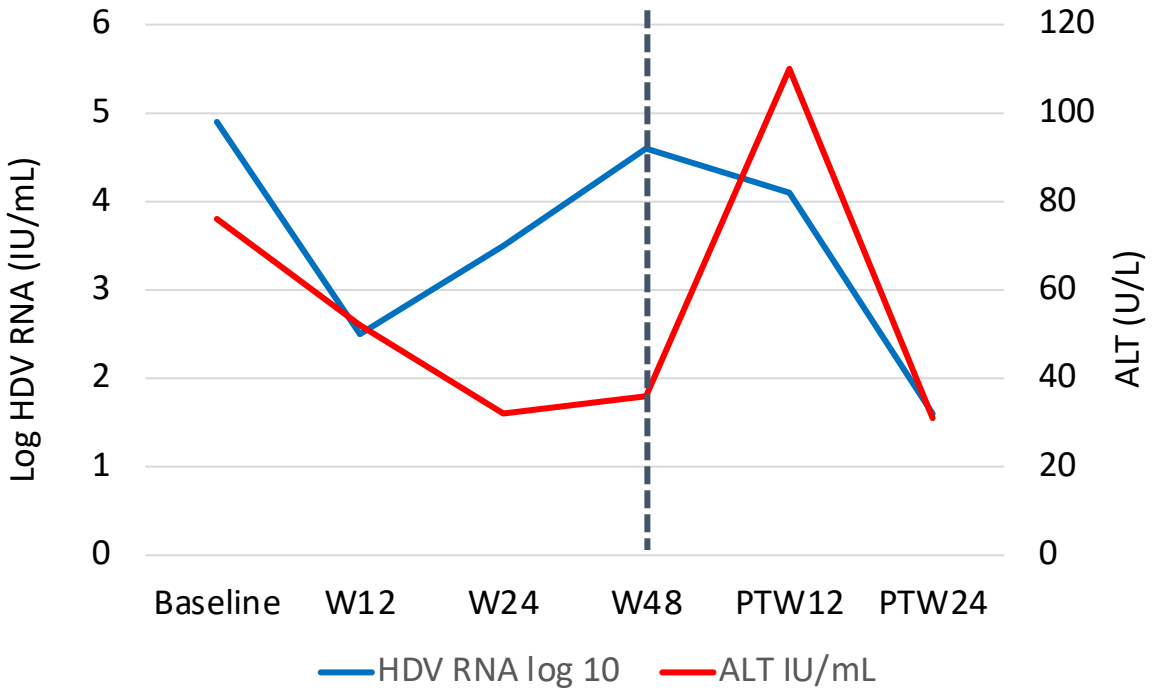




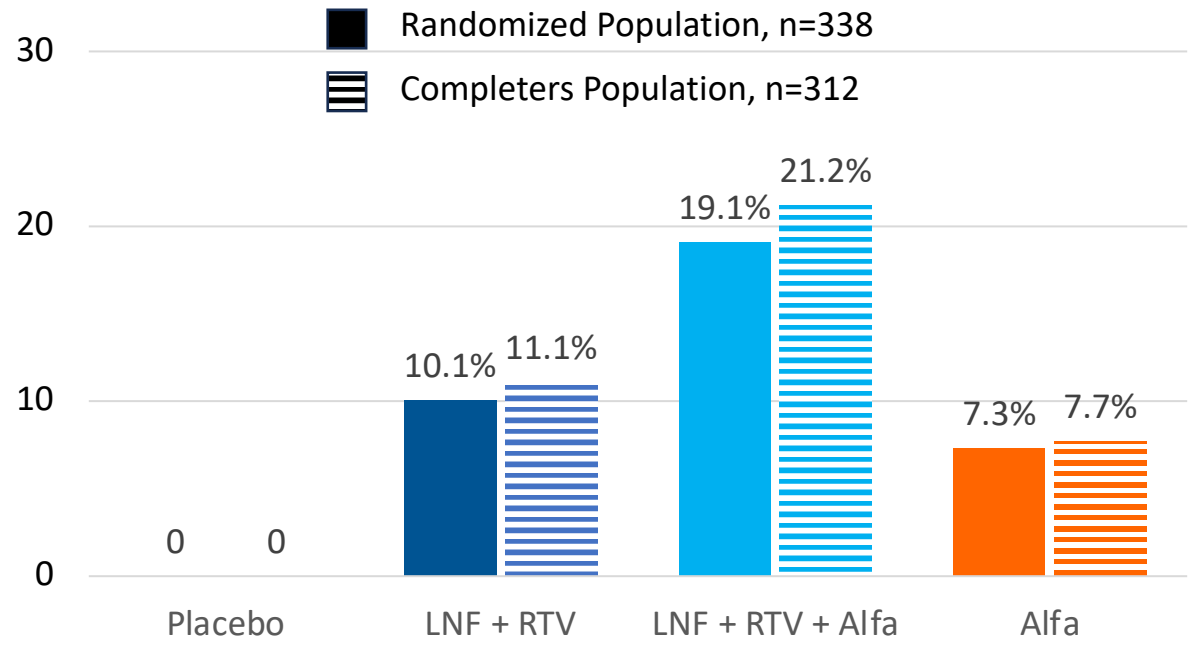
Beneficial Post-treatment Flares

- WELL-TOLERATED, WITHOUT SIGNS OF DECOMPENSATION
- TRANSIENT ALT ELEVATIONS ASSOCIATED WITH HDV RNA DECLINE

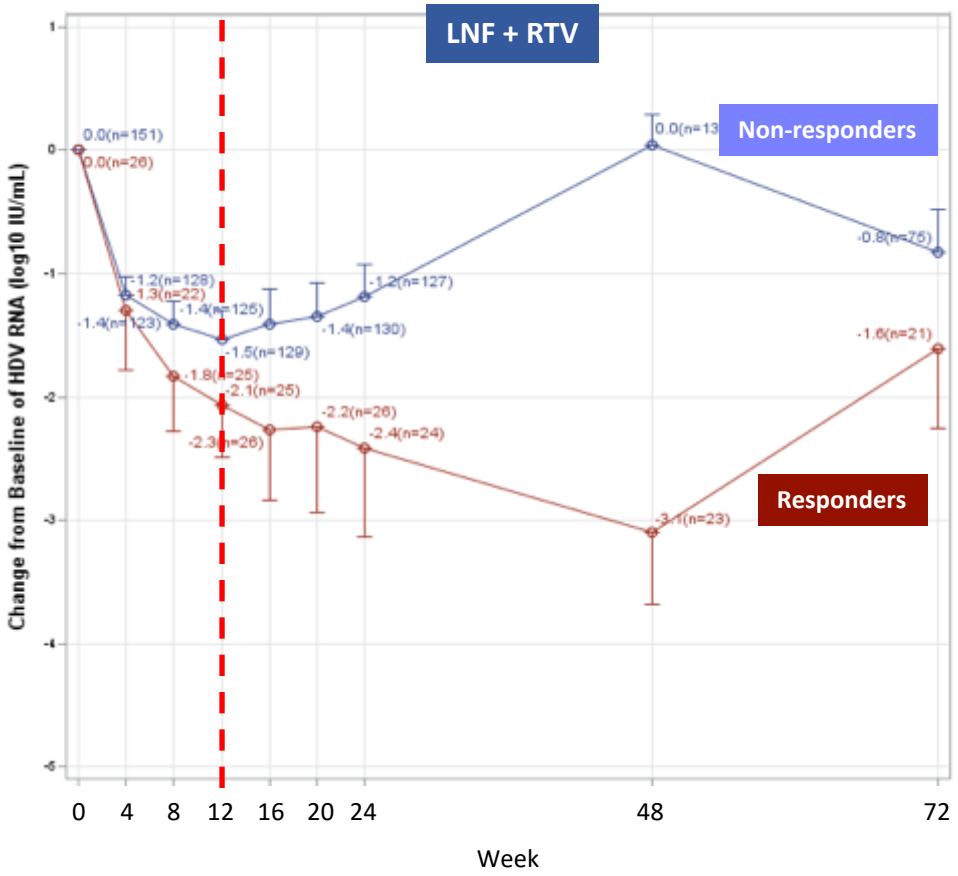
HDV RNA & ALT Kinetics

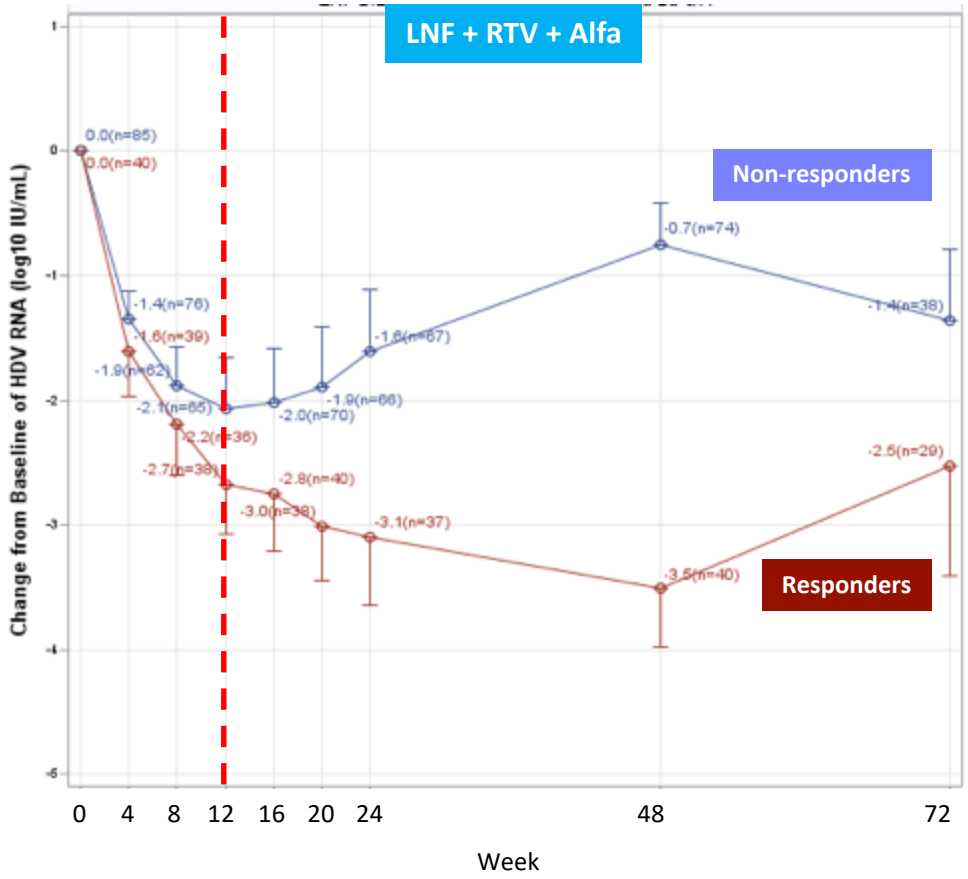


Beneficial Post-Treatment Flares



Responder/Non-Responder Analysis - Virologic





Overall Safety through Week 48

BOTH LONAFARNIB-TREATMENT REGIMENS WERE WELL-TOLERATED

	N (%)				
	Placebo (n=52)	LNF + RTV (n=178)	LNF + RTV + Alfa (n=125)	Alfa (n=50)	Total (N=405)
Discontinuations	10 (19)	34 (19)	22 (18)	11 (21)	77 (19)
Patients with ≥ 1 dose interruption/missed dose	14 (27)	76 (43)	64 (51)	27 (54)	181 (45)
Patients ≥ 1 TEAE	37 (71)	168 (94)	120 (96)	48 (96)	373 (92)
Patients with serious TEAE	2 (4)	15 (8)	18 (14)	5 (10)	40 (10)
Patients with ≥ 1 TEAE leading to death	0	1 (1)[1]	1 (1)[1]	1 (2)[2]	3 (1)

[1]Deemed unrelated to treatment
[2]Deemed related to treatment

Dose Modifications

33% OF PATIENTS DOSE REDUCED; ~50% SUBSEQUENTLY DOSE INCREASED

	N (%)				
	Placebo (n=52)	LNF + RTV (n=178)	LNF + RTV + Alfa (n=125)	Alfa (n=52)	Total (N=407)
Patients who dose reduced, n (%)	0	46 (26)	65 (52)	22 (44)	133 (33)
Patients who subsequently dose increased, n (%)	0	26 (57)	35 (54)	10 (46)	71 (53)
Patients with ≥ 1 dose interruption/missed dose, n (%)	14 (27)	76 (43)	64 (51)	27 (54)	181 (45)
Patients who subsequently restarted, n (%)	11 (79)	72 (95)	57 (89)	25 (93)	165 (91)
Reason for first dose interruption/missed dose					
Adverse Event, n (%)	2 (4)	19 (11)	34 (27)	10 (20)	65 (16)
Other (drug availability, etc) , n (%)	12 (23)	57 (32)	30 (24)	17 (34)	116 (29)

Summary and Conclusions

- Both LNF arms achieved the composite primary endpoint vs placebo
- Key secondary virological and biochemical endpoints were also met
- Statistically significant improvement in histology in the combination arm
  - Further strengthens assessment of the potential utility/benefit of treatment
  - Could be predictive of improved long-term clinical outcomes
- Both lonafarnib-treatment regimens were well-tolerated
- Encouraging 24-week off-treatment response rate exceeds EOT response rates, suggests finite, oral-based therapy may be possible in a subset of patients with CHDV

Acknowledgments

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