Bulevirtide mono and combo in clinical trials

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GHiE Gastroenterologie Hepatologie Infektiologie Endokrinologie

MHH

Medizinische Hochschule Hannover

Conflicts of Interest

Honoraria for consulting or speaking (last 5 years):

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Maura Dandri, Lena Allweiss

HDV-1000

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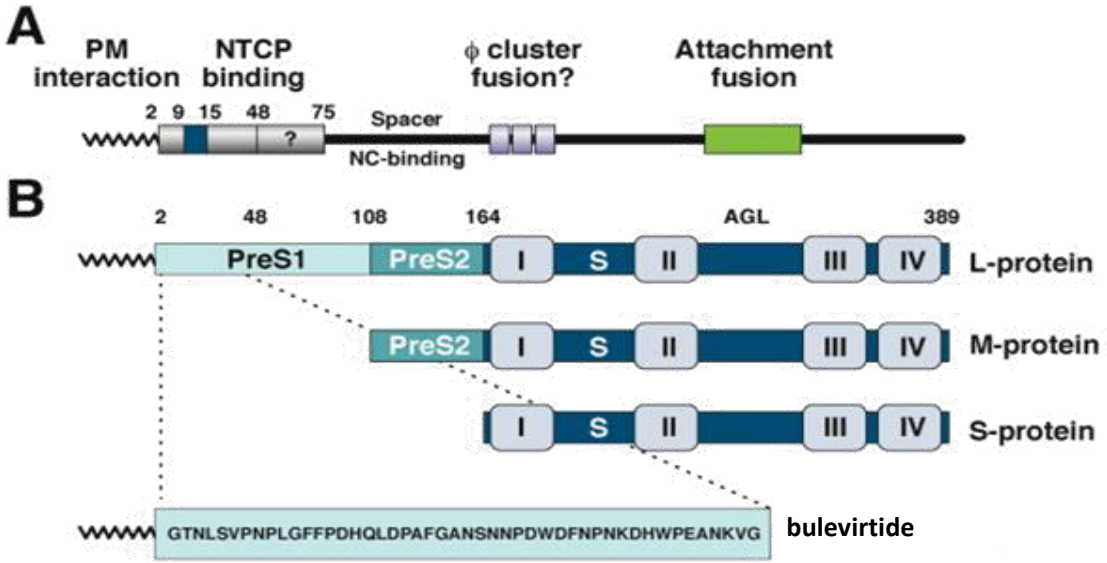
K Aggarwal, S. Aleman, F. Caruntu,

K. Deterding, A. Wranke

THE D-SOLVE Consortium

Pietro Lampertico, Markus Cornberg, Jennifer Debarry, Helenie Kefalakes, Lisa Sandmann, Yang Li, Soo Aleman, Joachim Lupberger, Niklas Björkstrom, Thomas Baumert, Florin Caruntu

Bulevirtide (Myrcludex B)

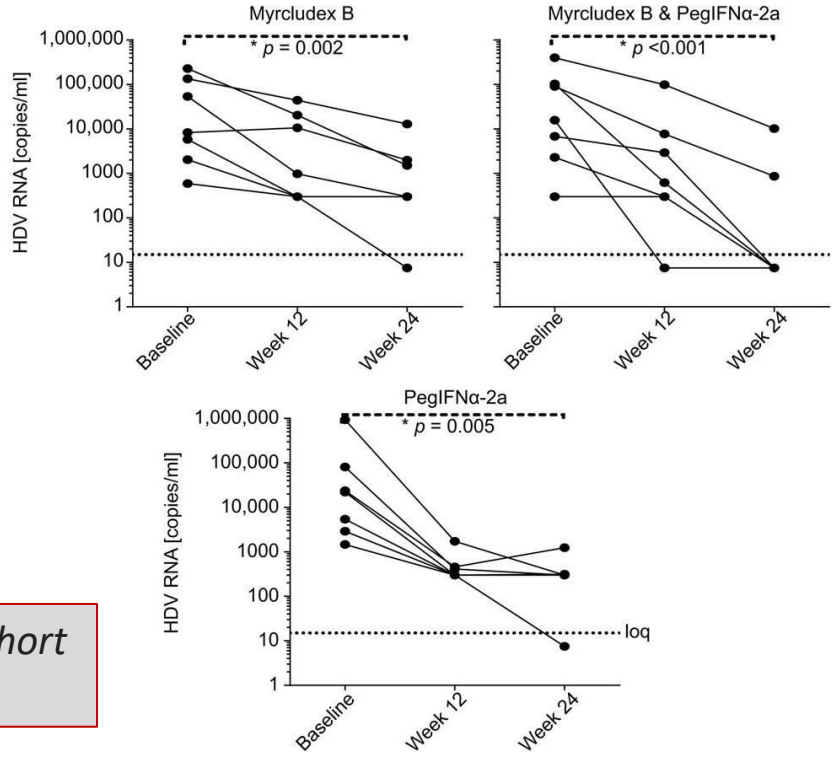


- Myrcludex B specifically binds to NTCP at the basolateral membrane of differentiated hepatocytes.
- Myrcludex B shows strong inhibitory potential for HBV and HDV infection (IC_{50} ca 80 pM in PHH).
- It exclusively targets parenchymal liver cells.

Urban et al., Gastroenterology 2014;147:48-64

Phase 2a pilot study MYR-201

- 24 patients
- BLV
  BLV/PEG-IFNa
  PEG-IFNa
- 24 weeks of treatment



ALT decreased significantly in the Myrcludex B cohort (six of eight patients)

Bogomolov et al. J Hepatol 2016, Sep;65(3):490-8

Bulevirtide for Hepatitis D: The “MYR”-Trials

➢ 202	n=118	24 weeks	4 arms	Dose finding (BLV 2mg vs. 5mg vs. 10 mg)
➢ 203	n=90	48 weeks	4+2 arms	BLV monotherapy vs. combination with PEG-IFNa
➢ 204	n=175	96 weeks	4 arms	BLV+PEG-IFNa followed by BLV monotherapy
➢ 301	n=150	96-144 w.	3 arms	BLV 2 mg vs. 10mg; 96 vs. 144 weeks

BLV Clinical Trials: Patient characteristics

Baseline variables	MYR202 (n=118)	MYR203 (n=90)	MYR204 (n=175)	MYR301 (n=150)	Total (N=532)
Age, yrs*	40.2 (9.5)	36 (18-62)	41 (8.7)	41.8 (8.4)	40 (18-66)
Male	79 (67)	57 (63.3%)	124 (71.3)	86 (57%)	346 (65%)
Race, white	101 (86)	88 (97.8%)	151 (87)	124 (83%)	464 (87%)
Cirrhosis	59 (50%)	15 (16.7%)	60 (34.5)	71 (47%)	203 (38)
Previous pegIFNα	67 (56.8%)	5 (5.6%)	84 (48.3)	84 (56%)	288 (54%)
ALT, U/L)**	116 (79.5)	119.5±119,4	114 (94.8)	111 (69)	114 (111)
HDV RNA, log IU/ml**	5.31 (1.26)	5.61±1.45	5.3 (1.24)	5.0 (1.4)	5.3 (1.32)
HBsAg, log IU/ml**	3.98 (0.57)	4.10±0.66	3.7 (0.6)	3.7 (0.52)	3.8 (0.61)
HBeAg positive	11 (9.3)	9 (10%)	19 (11)	15 (10%)	54 (10)
Fibroscan, KPa**	16.0 (8.7)	11.5 (5.8)	13.1 (7.7)	14.7 (8.8)	12.2 (6.22)

Lampertico et al. J Hepatol. 2022 Jun 22:S0168-8278(22)00373-7

Bulevirtide monotherapy (+/- anti-HBV NUCs)

MYR202, MYR203 arms D&F, MYR204 arm D, MYR301

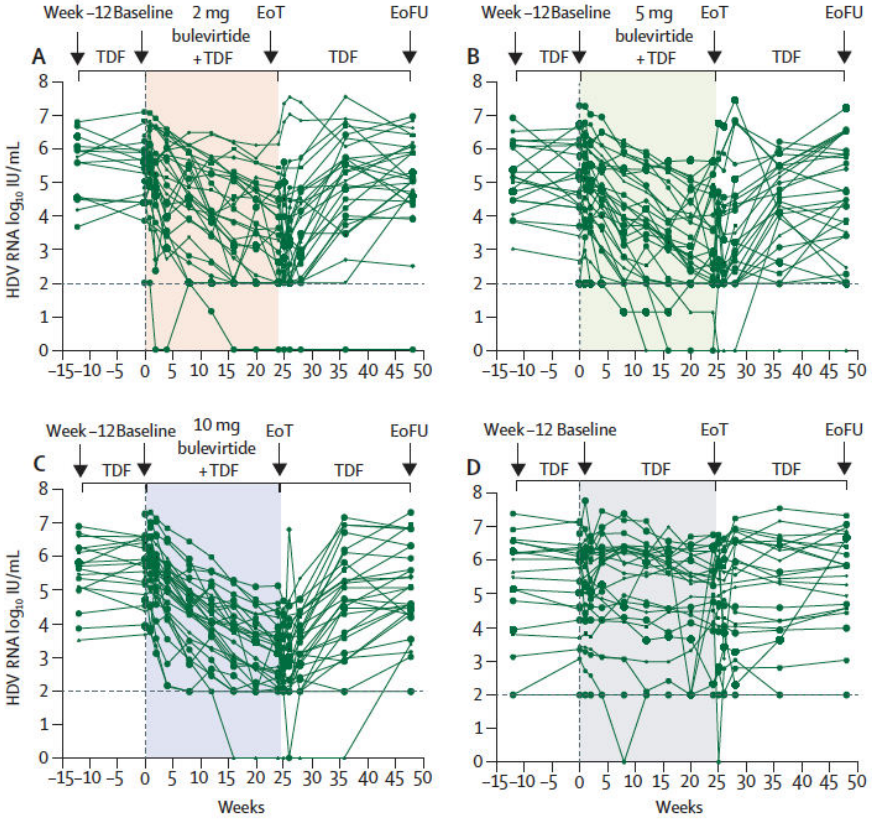
MYR 202

Safety and efficacy of bulevirtide in combination with tenofovir disoproxil fumarate in patients with hepatitis B virus and hepatitis D virus coinfection (MYR202): a multicentre, randomised, parallel-group, open-label, phase 2 trial

Heiner Wedemeyer, Katrin Schöneweis, Pavel Bogomolov, Antje Blank, Natalia Voronkova, Tatiana Stepanova, Olga Sagalova, Vladimir Chulanov, Marina Osipenko, Viacheslav Morozov, Natalia Geyvandova, Snezhana Sleptsova, Igor G Bakulin, Ilsiyar Khaertynova, Marina Rusanova, Anita Pathil, Uta Merle, Birgit Bremer, Lena Allweiss, Florian A Lempp, Kerstin Port, Mathias Haag, Matthias Schwab, Julian Schulze zur Wiesch, Markus Cornberg, Walter E Haefeli, Maura Dandri, Alexander Alexandrov, Stephan Urban

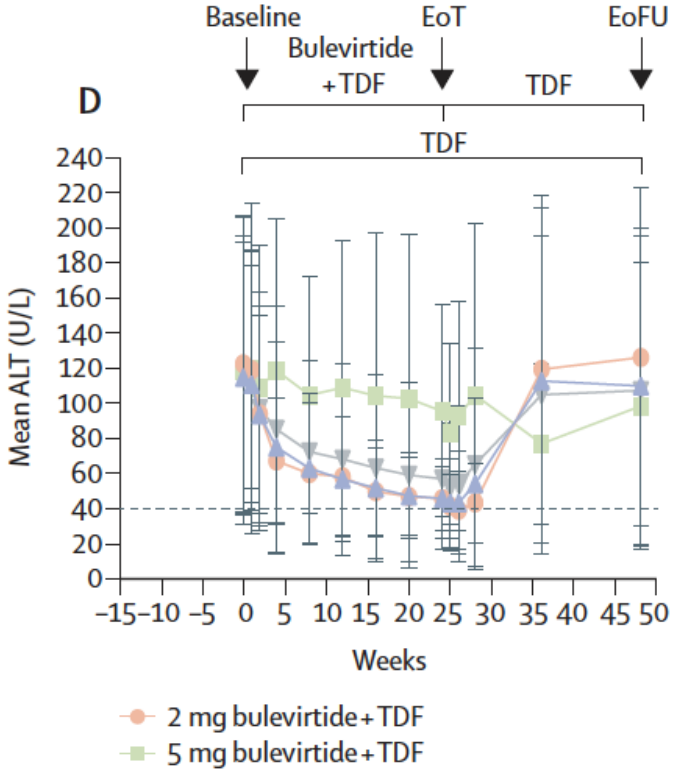
Lancet Infect Dis. 2022 Sep 13:S1473-3099(22)00318-8. doi: 10.1016/S1473-3099(22)00318-8. Online ahead of print.PMID: 36113537

MYR202: HDV RNA decline



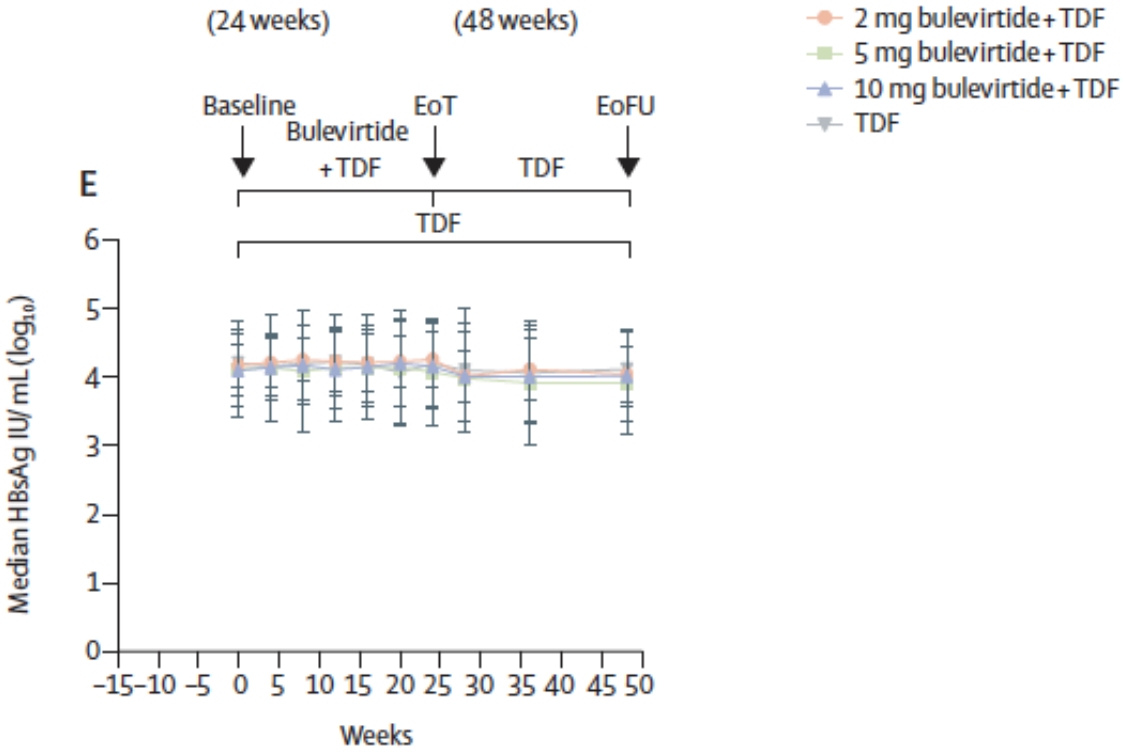
Wedemeyer et al. Lancet Infect Dis 2022 Sep 13:S1473-3099(22)00318-8

MYR202: ALT Response



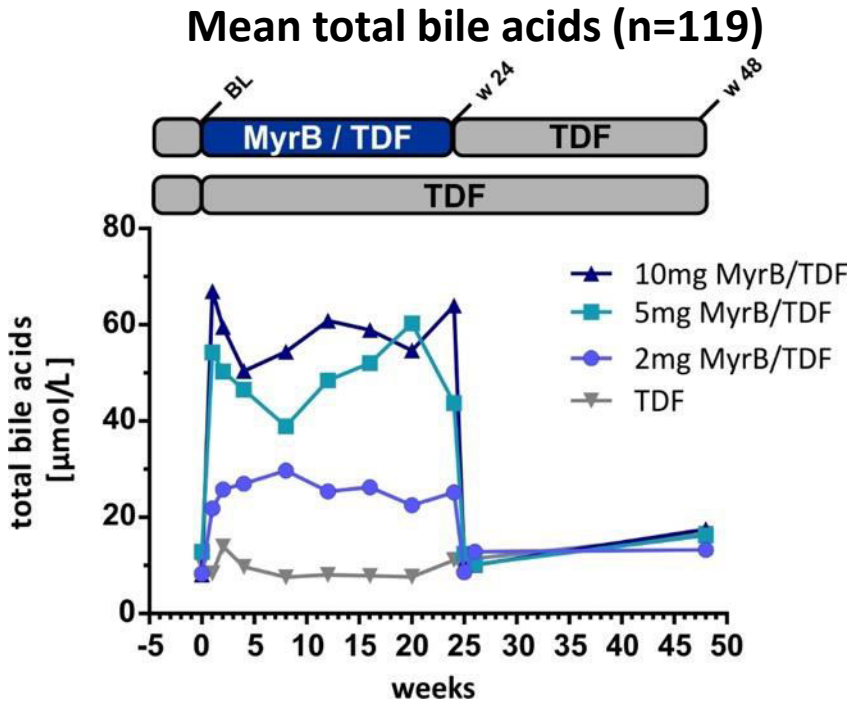
Wedemeyer et al. Lancet Infect Dis 2022 Sep 13:S1473-3099(22)00318-8

MYR202: HBsAg



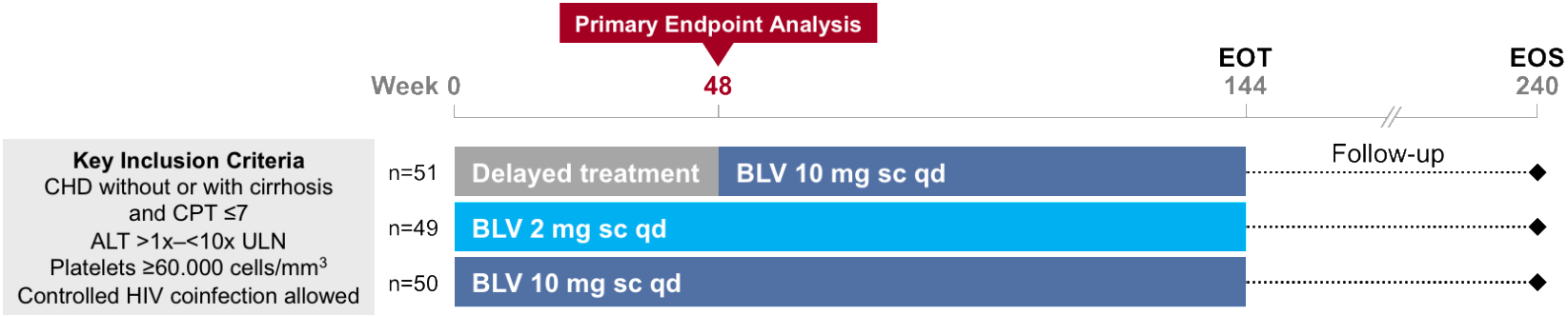
Wedemeyer et al. Lancet Infect Dis 2022 Sep 13:S1473-3099(22)00318-8

Bulevirtide treatment induces bile acid increase



Wedemeyer et al. Lancet Infect Dis 2022 Sep 13:S1473-3099(22)00318-8

MYR 301



- Multicenter, open-label, randomized, Phase 3 study (ClinicalTrials.gov NCT03852719) conducted in 4 countries (Germany, Italy, Russian Federation, and Sweden)

Bulevirtide 301 study:

Treatment was well tolerated – very few drop-outs

Aleman et al.,

High Rates of Adherence to Bulevirtide Monotherapy for Chronic Hepatitis Delta Through 96 Weeks: Results From an Interim Analysis of the Phase 3 Study MYR301

Delta Cure 2024; Poster 41

MYR301

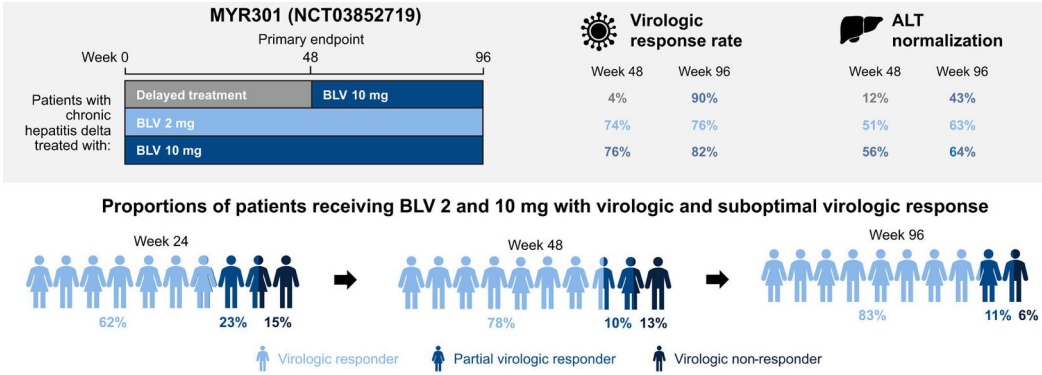
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

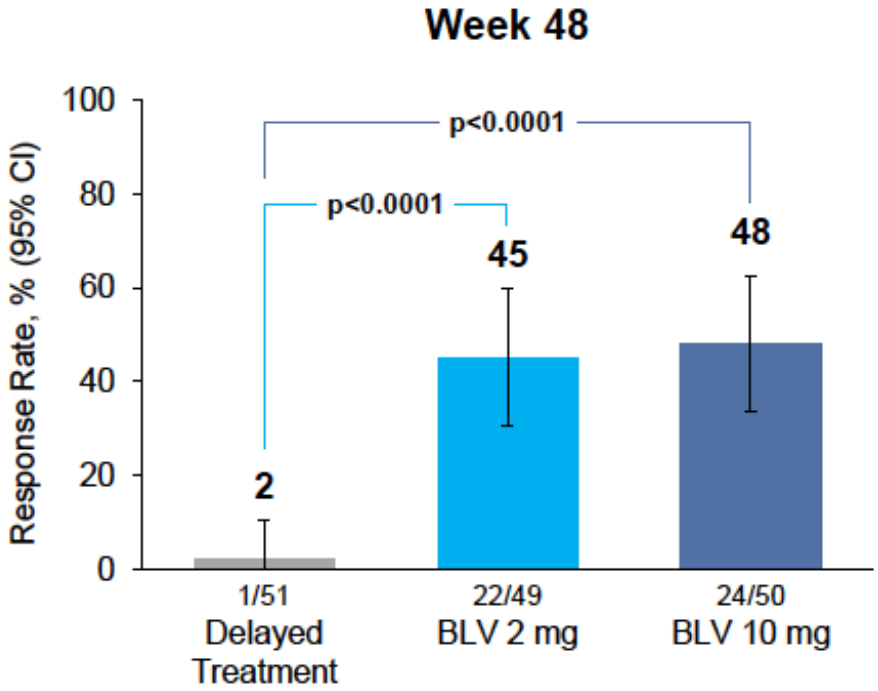
A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D

H. Wedemeyer, S. Aleman, M.R. Brunetto, A. Blank, P. Andreone, P. Bogomolov, V. Chulanov, N. Mamonova, N. Geyvandova, V. Morozov, O. Sagalova, T. Stepanova, A. Berger, D. Manuilov, V. Suri, Q. An, B. Da, J. Flaherty, A. Osinusi, Y. Liu, U. Merle, J.S.. Wiesch, S. Zeuzem, S. Ciesek, M. Cornberg, and P. Lampertico, for the MYR 301 Study Group*

EASL | JOURNAL OF HEPATOLOGY



MYR301: Combined Response (virological and biochemical)

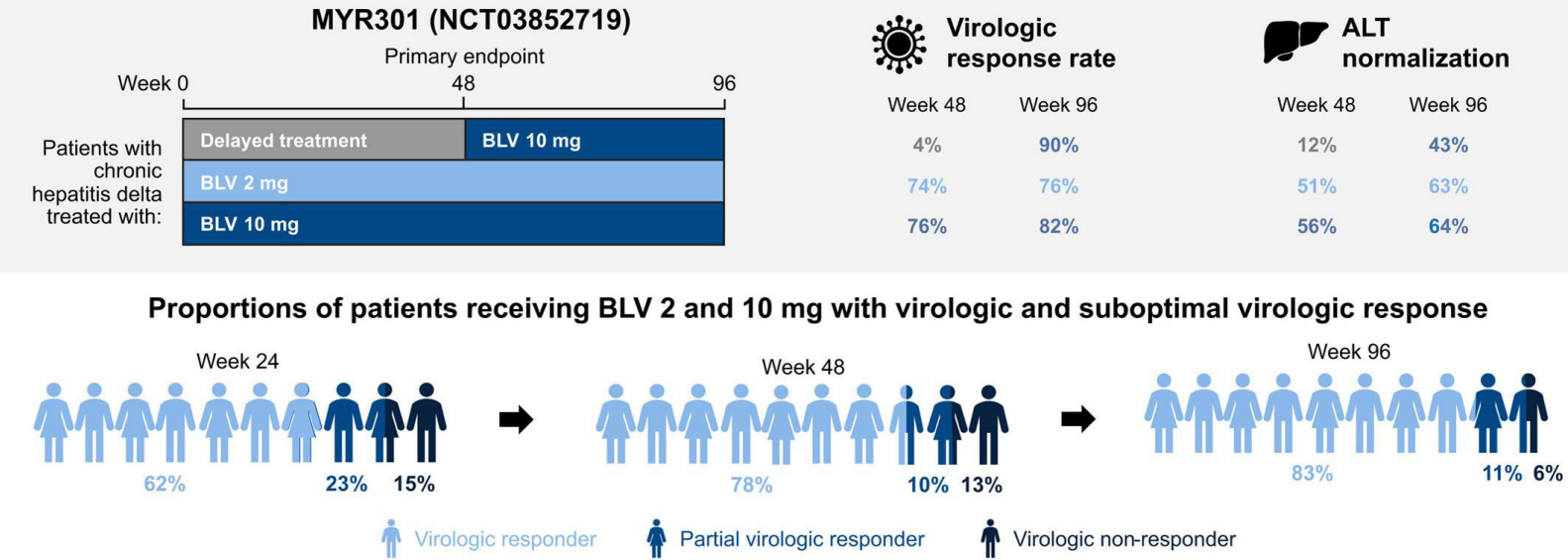


Wedemeyer et al. EASL 2021. #LBP-2730

Wedemeyer…, Lampertico N Engl J Med 2023;389:22-32

Bulevirtide 301 study:

Response until week 96



Wedemeyer et al., J Hepatol 2024 epub

Bulevirtide 301 study:

Response until week 144

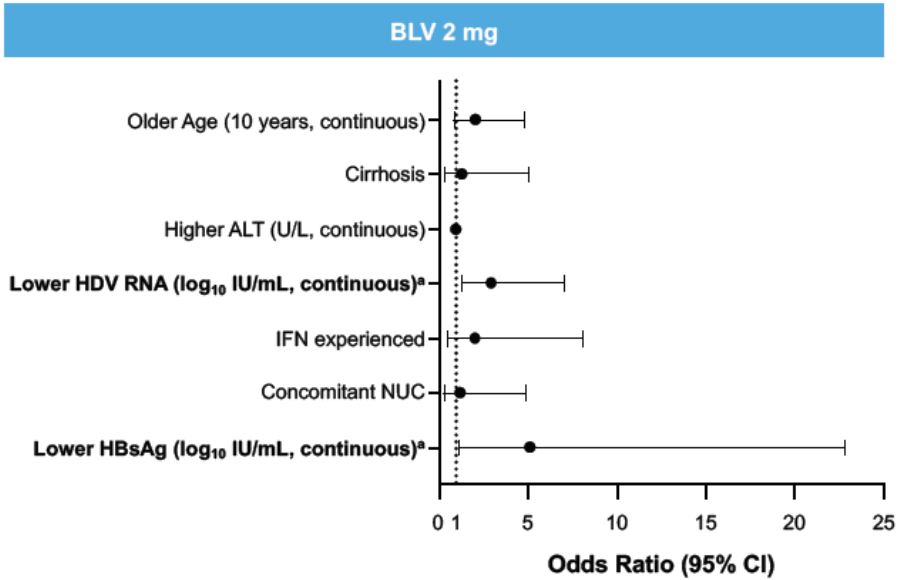
301 study: HDV RNA undetectable

(Lampertico et al. EASL 2024 and DeltaCure 2024 Poster 27)

	week 48	week 96	week 144
2mg	12%	20%	29%
10mg	20%	36%	50%

Bulevirtide 301 study:

Similar reponse likelihood regardless of age, cirrhosis, NUC therapy or previous IFNa exposure



Lampertico et al. EASL 2024 and DeltaCure 2024 Poster 27

Bulevirtide 301 study: **off-treatment data?**

Just wait for less than 1 hour!

Soo Aleman et al.,

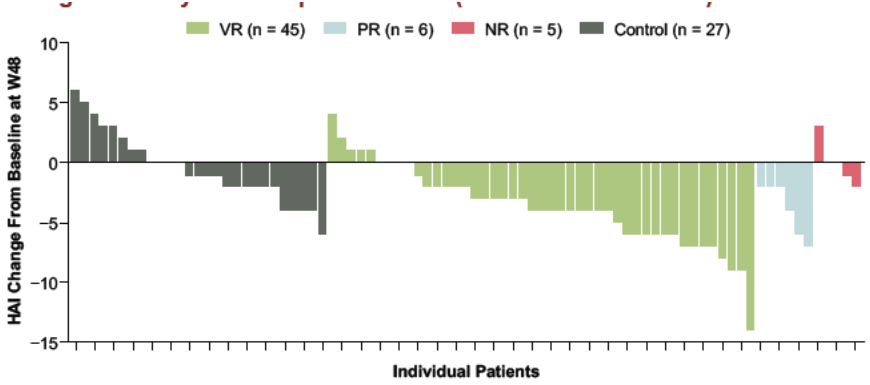
DeltaCure 2024 Poster 43 and oral presentation at 18.25 pm

*Efficacy and safety of BLV monotherapy for chronic hepatitis delta: **post treatment results through 24 weeks afer the end of treatment** from an interim analysis of a randomized Phase 3 study MYR301*

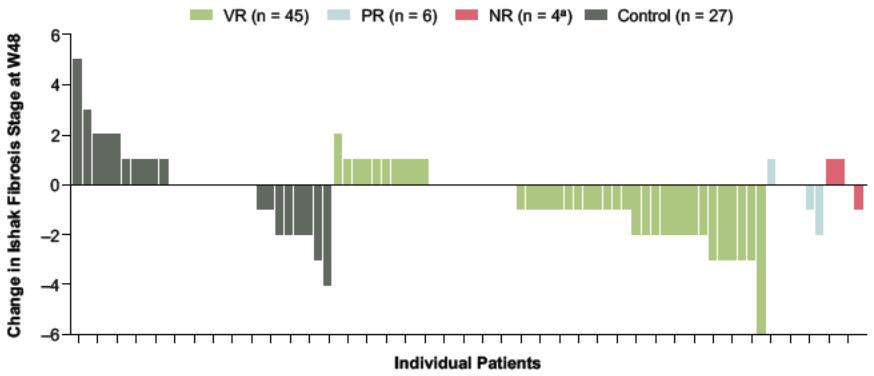
Bulevirtide 301 study:

Histology *(paired biopsy week 48)*

Inflammation



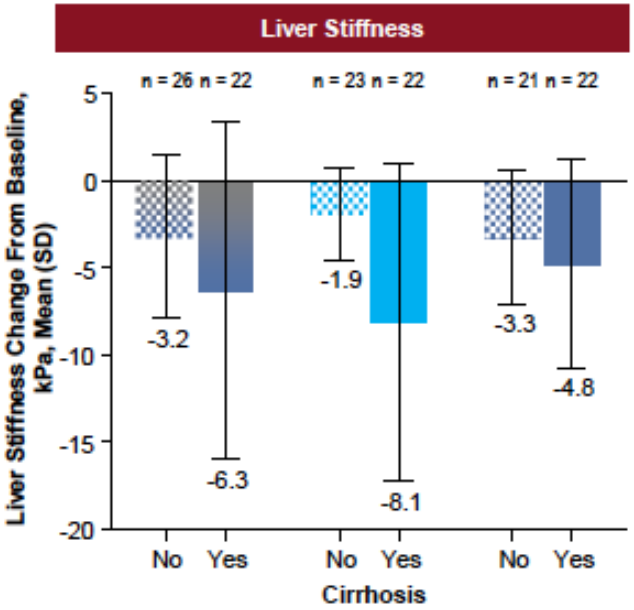
Fibrosis



Lampertico et al., EASL 2024 and Delta Cure Poster 32

Bulevirtide 301 study:

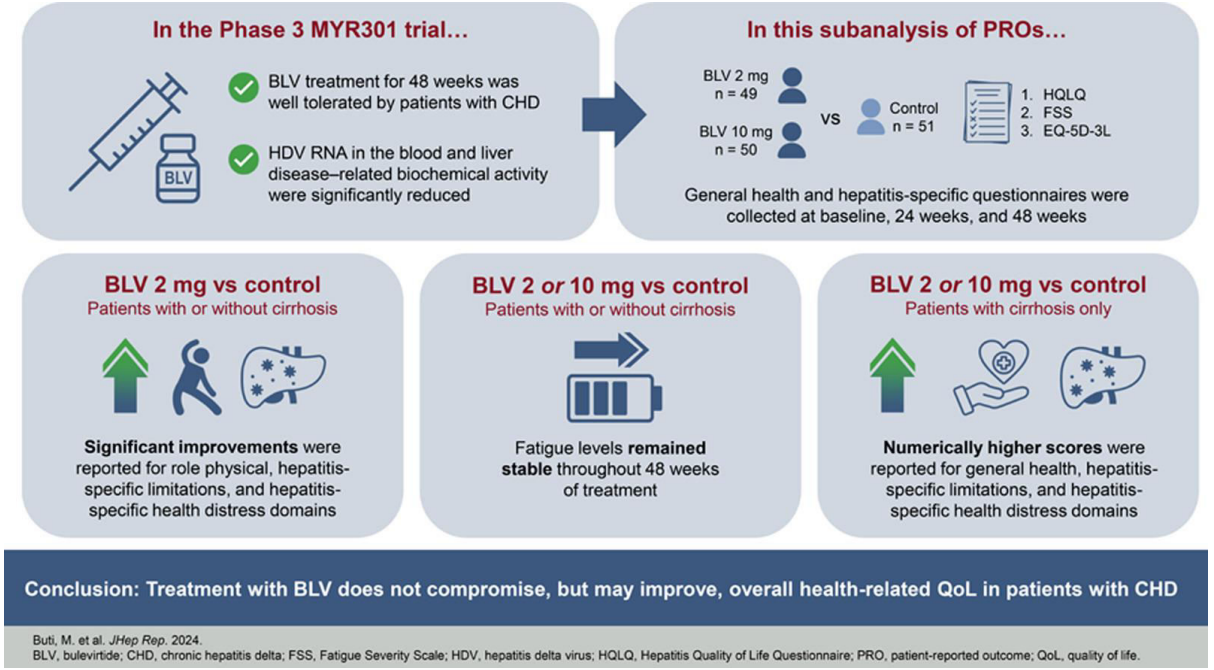
Liver elastography



Aleman et al., EASL 2024

Bulevirtide 301 study:

Patient reported outcomes week 48



Buti, M. et al. *JHep Rep.* 2024.
BLV, bulevirtide; CHD, chronic hepatitis delta; FSS, Fatigue Severity Scale; HDV, hepatitis delta virus; HQLQ, Hepatitis Quality of Life Questionnaire; PRO, patient-reported outcome; QoL, quality of life.

Buti et al., J Hepatol. 2024 Jul 13:S0168-8278(24)02337-7.

Bulevirtide 301 study:

Patient reported outcomes until week 96

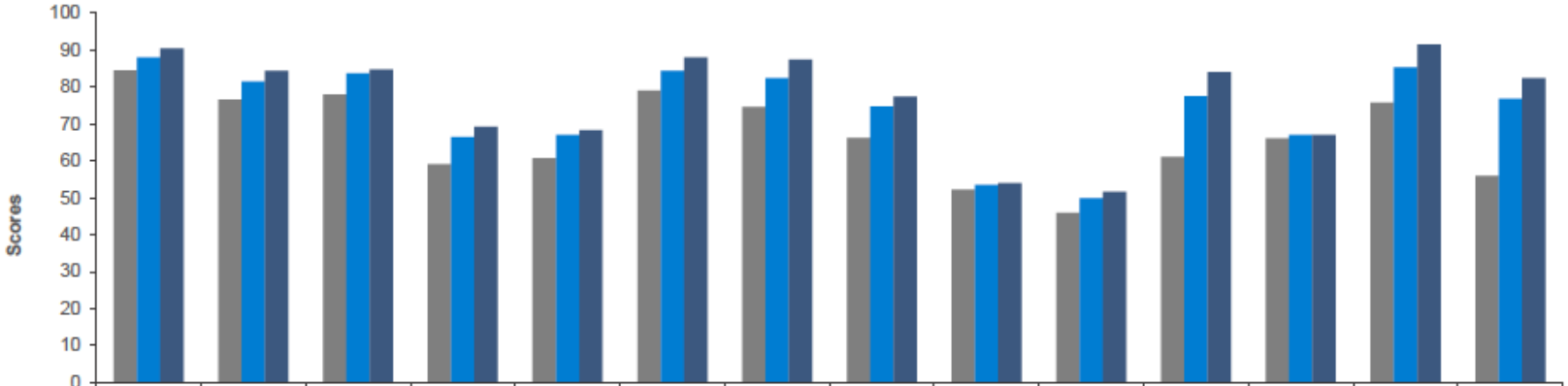
Buti et al.,

Patient-Reported Outcomes Among Patients With Chronic Hepatitis Delta Treated With Bulevirtide 2 mg: A Long-Term Analysis of the Phase 3 MYR301 Trial at 96 Weeks

Delta Cure 2024 Poster 37

Bulevirtide 301 study:

Patient reported outcomes until week 96

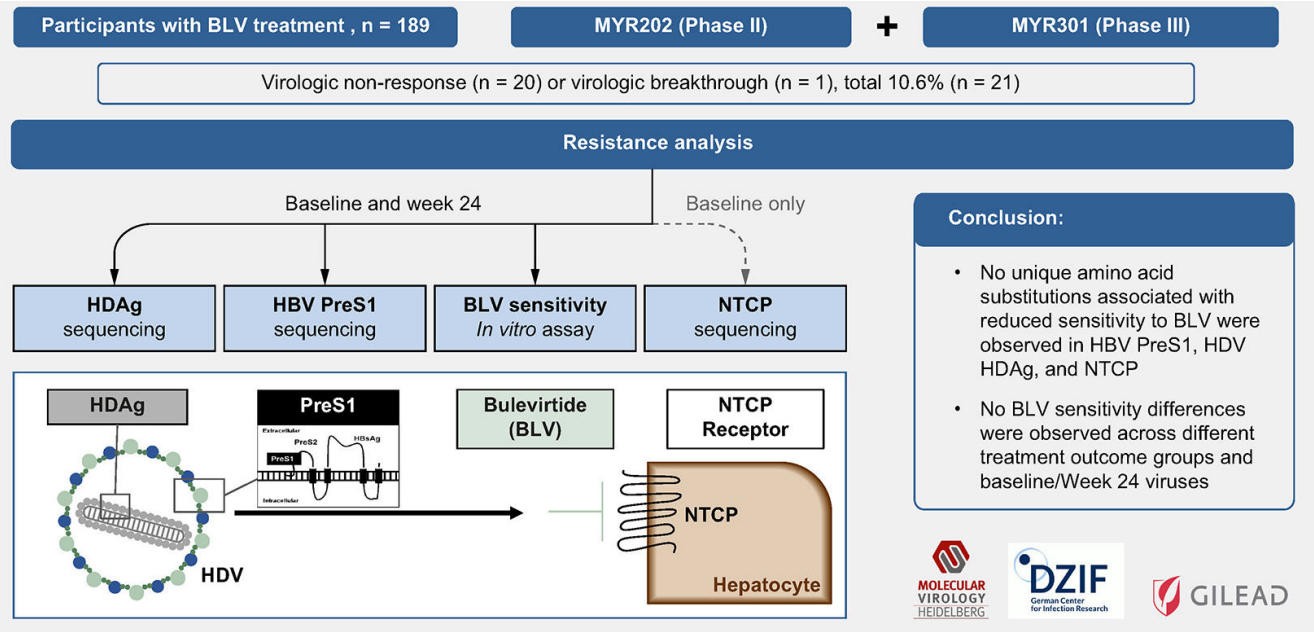


	Physical Functioning	Role Physical	Bodily Pain	General Health	Vitality Scale	Social Functioning	Role Emotional	Mental Health	PCS	MCS	Health Distress Scale	Positive Well-being Scale	HS Limitations Scale	HS Health Distress Scale
BL	84.59	76.66	77.98	59.12	60.71	79.08	74.66	66.22	52.25	45.92	61.12	66.12	75.78	56.02
48W	88.02	81.51	83.73	66.54	67.02	84.38	82.47	74.76	53.53	49.89	77.60	67.08	85.42	76.88
96W	90.43	84.38	84.76	69.24	68.34	88.04	87.50	77.39	54.00	51.71	84.13	67.07	91.59	82.39

Buti et al., Delta Cure 2024 Poster 37

Bulevirtide 301 study:

Treatment failures? Resistance?



Hollnberger et al., J Hepatol 2023 Sep;79(3):657-665

Bulevirtide 301 study:

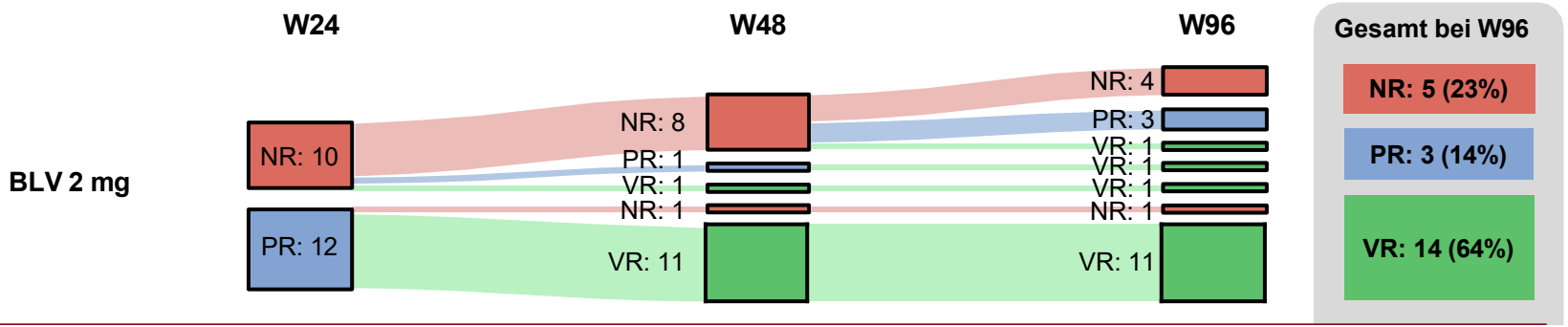
Continued treatment of partial responders or nonresponder?

Lampertico et al.,

Continued Treatment of Early Virologic Non-responders or Partial Responders With Bulevirtide Monotherapy for Chronic Hepatitis Delta Leads to Improvement in Virologic and Biochemical Responses. Results From an Integrated Analysis at Week 96

Delta Cure 2024, Poster 26

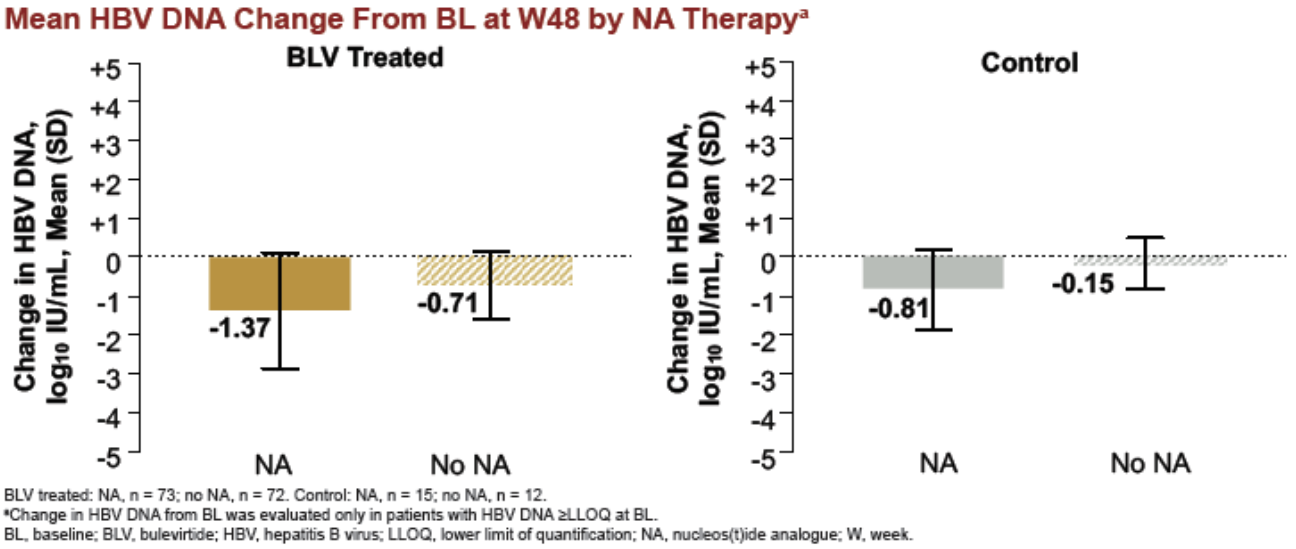
Bulevirtide 301 study:
responses increase in w24 NR/PR



BLV, bulevirtide; NR, non-responder; PR, partial responder; VR, virologic responder; W, week.

Bulevirtide 301 study:

Effects on HBV markers



BLV treated: NA, n = 73; no NA, n = 72. Control: NA, n = 15; no NA, n = 12.
[a]Change in HBV DNA from BL was evaluated only in patients with HBV DNA ≥LLOQ at BL.
BL, baseline; BLV, bulevirtide; HBV, hepatitis B virus; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; W, week.

Lampertico et al., EASL 2024

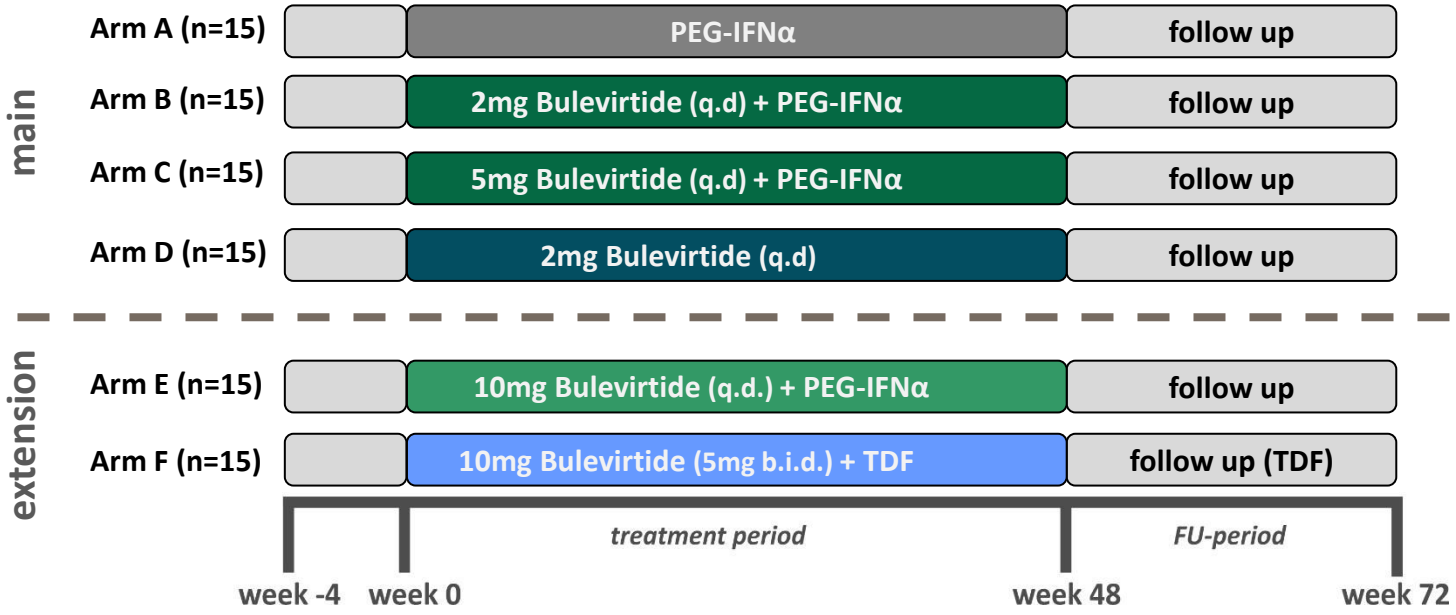
PEG-IFNa + BLV combination therapy

MYR 203

Wedemeyer et al., EASL ILC 2019 & 2020 (!!!)

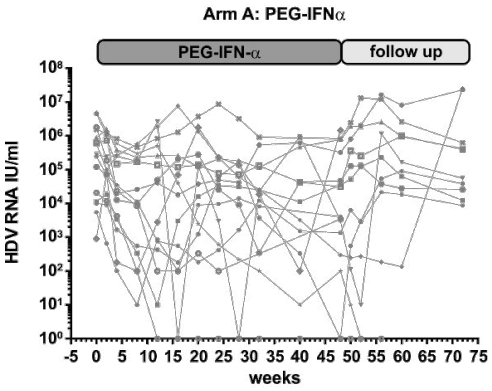
Reviewers are likely in the room: Please be nice,
this data set should become available to the comunity ☺

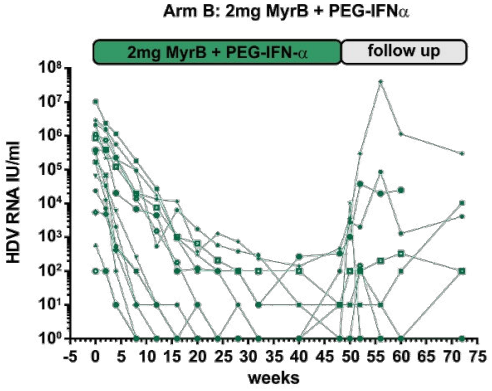
MYR203 Study Design

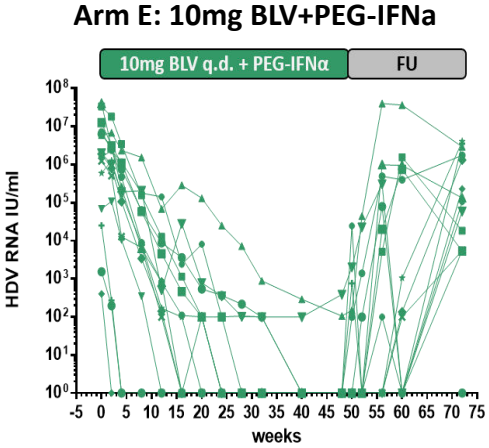


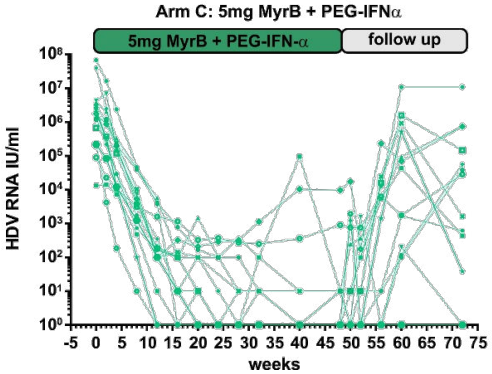
Wedemeyer et al. EASL 2019 & EASL 2020

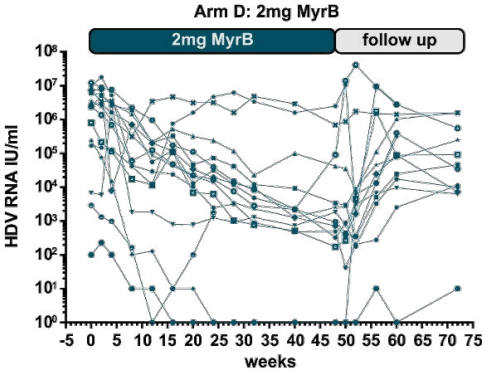
Myr203 Study: HDV RNA







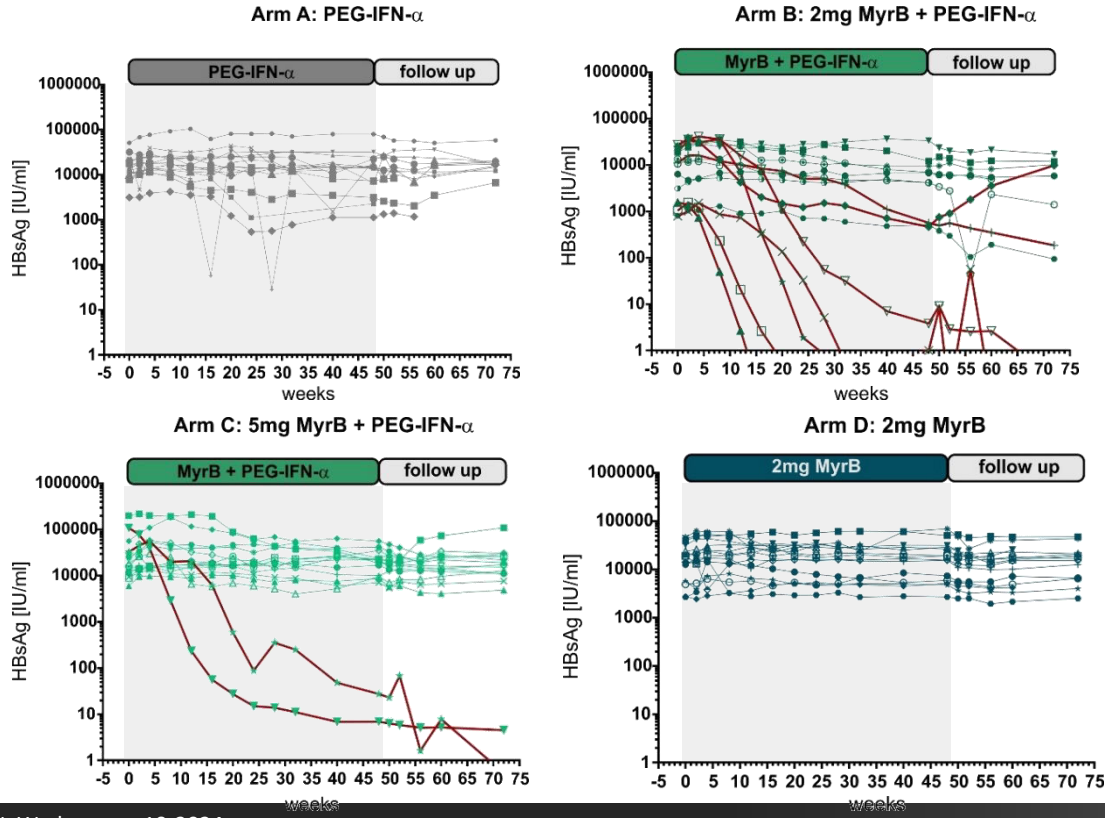


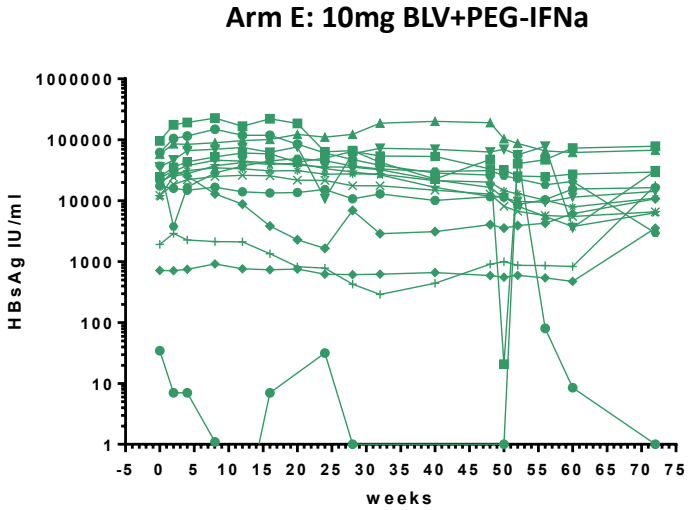


Virological response: week 72	Primary endpoint: undetectable HDV RNA
PEG-IFNα	0.0%
2mg BLV + PEG-IFNα	53.3%
5mg BLV + PEG-IFNα	26.7%
10mg BLV + PEG-IFNα	6.7%

Wedemeyer et al. EASL-ILC 2019 & ILC2020

MYR203: HBsAg Decline

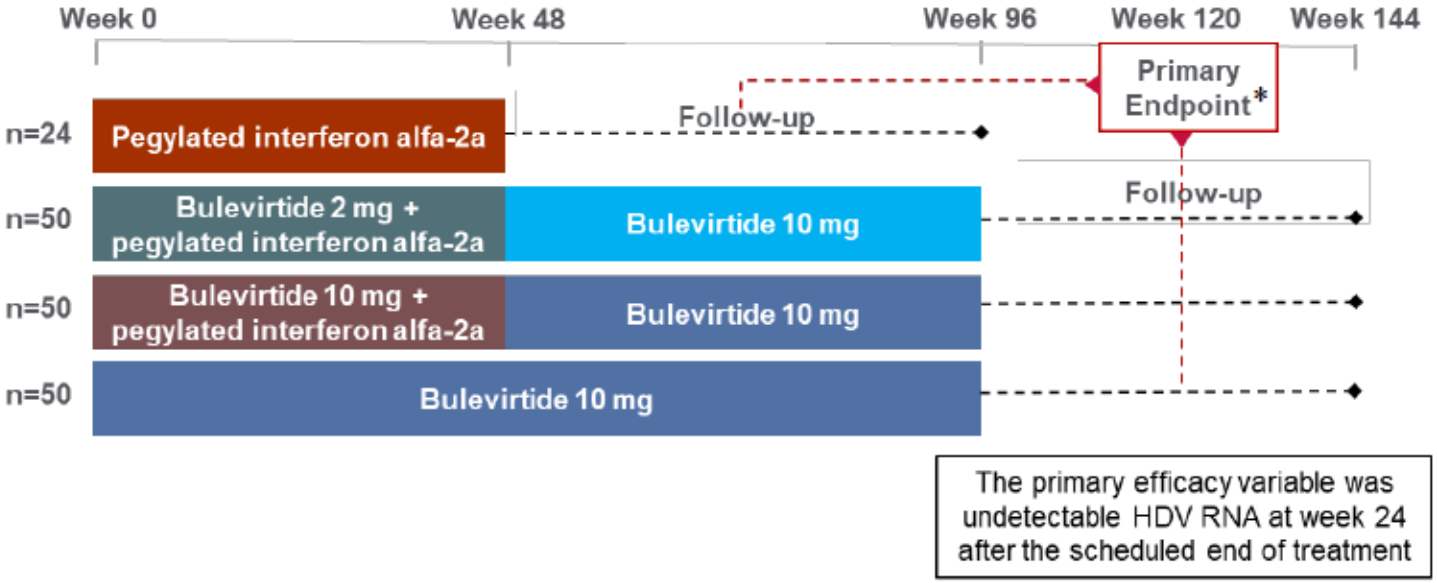




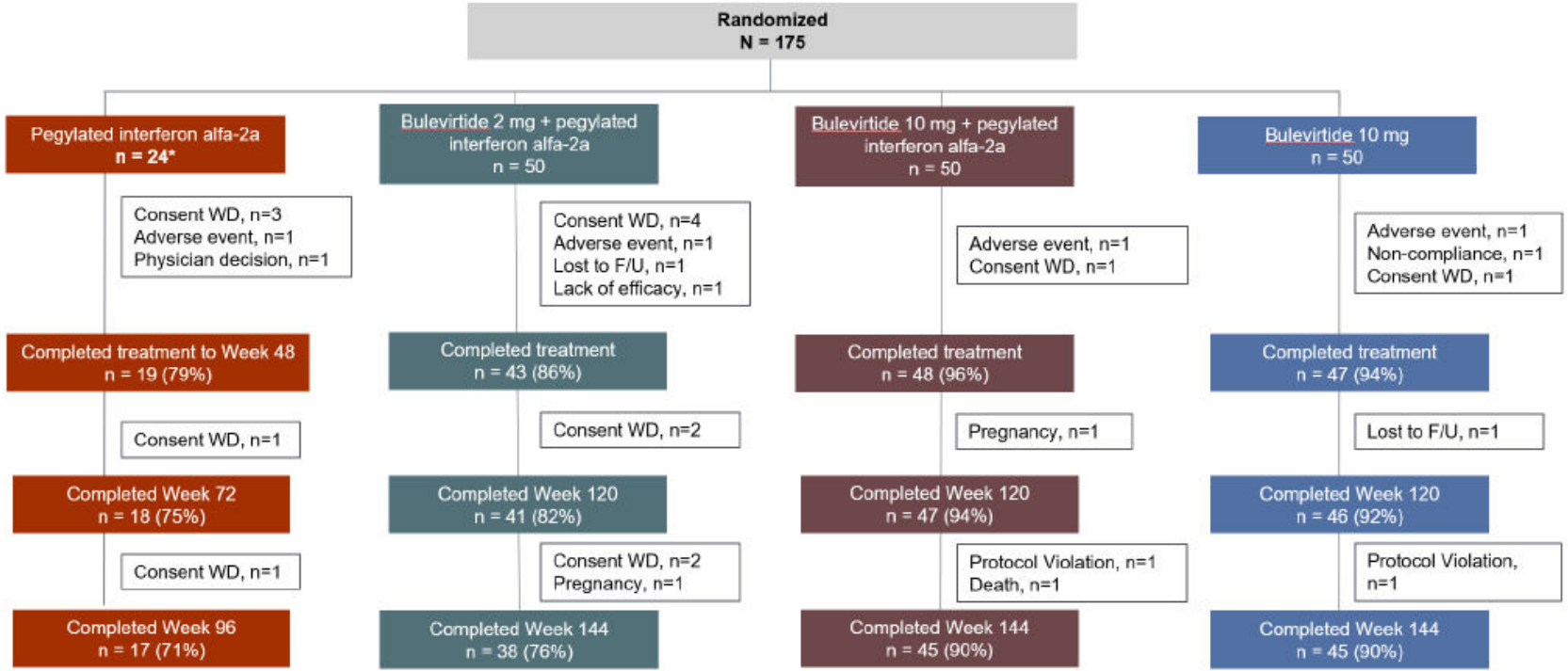
Wedemeyer et al. EASL ILC 2019 & ILC2020

MYR 204

MYR 204


Week 0
Week 48
Week 96
Week 120
Week 144
Primary Endpoint*
n=24
Pegylated interferon alfa-2a
Follow-up
n=50
Bulevirtide 2 mg + pegylated interferon alfa-2a
Bulevirtide 10 mg
Follow-up
n=50
Bulevirtide 10 mg + pegylated interferon alfa-2a
Bulevirtide 10 mg
n=50
Bulevirtide 10 mg
The primary efficacy variable was undetectable HDV RNA at week 24 after the scheduled end of treatment

MYR 204



Asselah et al., NEJM 20242024 Jul 11;391(2):133-143.

The NEW ENGLAND JOURNAL of MEDICINE

Bulevirtide and Peginterferon for Chronic Hepatitis D

A PLAIN LANGUAGE SUMMARY

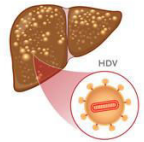
Based on the NEJM publication: Bulevirtide Combined with Pegylated Interferon for Chronic Hepatitis D by T. Asselah et al. (published June 6, 2024)

In this trial, researchers assessed bulevirtide, either alone or in combination with pegylated interferon (peginterferon) alfa-2a, as a potential finite treatment regimen for patients with chronic hepatitis D.

Chronic hepatitis D is the most severe form of chronic viral hepatitis. The risk of hepatocellular carcinoma among patients with chronic hepatitis D is two to six times that with hepatitis B virus infection, and the risk of death is two to three times that with hepatitis B.

WHY WAS THE TRIAL DONE?

Until recently, off-label use of peginterferon alfa was the only treatment for chronic hepatitis D. However, in a recent phase 3 trial, bulevirtide was associated with greater virologic response than no treatment in patients with this disease. The role of combination therapy with bulevirtide and peginterferon in chronic hepatitis D is uncertain.



HOW WAS THE TRIAL CONDUCTED?

174 patients with chronic hepatitis D received one of four treatments: subcutaneous peginterferon alfa-2a alone for 48 weeks; subcutaneous bulevirtide at one of two doses for 96 weeks, with peginterferon alfa-2a for the first 48 weeks; or subcutaneous bulevirtide alone for 96 weeks. The primary end point was an undetectable level of hepatitis D virus (HDV) RNA at 24 weeks after treatment ended. The primary comparison was between the 10-mg bulevirtide plus peginterferon alfa-2a group and the 10-mg bulevirtide-alone group.

PATIENTS

WHO	174 patients 18–65 years of age Men: 71%; Women: 29%
CLINICAL STATUS	Chronic hepatitis D Positive HDV RNA detected by polymerase chain reaction Alanine aminotransferase level above the upper limit of the normal range but less than 10 times above it

TRIAL DESIGN

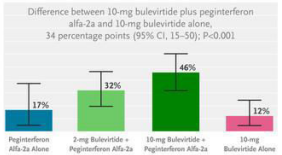
- PHASE 2B
- MULTICENTER
- OPEN-LABEL
- RANDOMIZED
- CONTROLLED

RESULTS

At 24 weeks after the end of treatment, the percentage of patients with undetectable HDV RNA was significantly greater in the 10-mg bulevirtide plus peginterferon alfa-2a group than in the 10-mg bulevirtide-alone group.

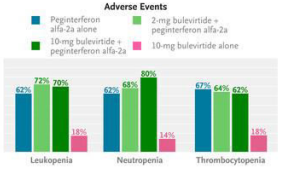
The percentage of patients with an undetectable HDV RNA level at 48 weeks after the end of treatment (a secondary end point) also favored 10-mg bulevirtide plus peginterferon alfa-2a.

Undetectable HDV RNA



The safety profile of bulevirtide plus peginterferon alfa-2a was consistent with the known safety profile of each drug. The most common adverse events were leukopenia, neutropenia, and thrombocytopenia.

Adverse Events



LIMITATIONS AND REMAINING QUESTIONS

- The trial was not designed to compare the two doses of bulevirtide.
- The trial was not powered to allow for comparisons between peginterferon alfa-2a alone and the other regimens.
- There was a lack of blinding to the intervention due to ethical reasons, such as daily placebo injections.

CONCLUSIONS

In patients with chronic hepatitis D, the combination of 10 mg of bulevirtide plus peginterferon alfa-2a was significantly more likely to result in an undetectable HDV RNA level at 24 weeks after the end of treatment than bulevirtide monotherapy.

LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

FURTHER INFORMATION

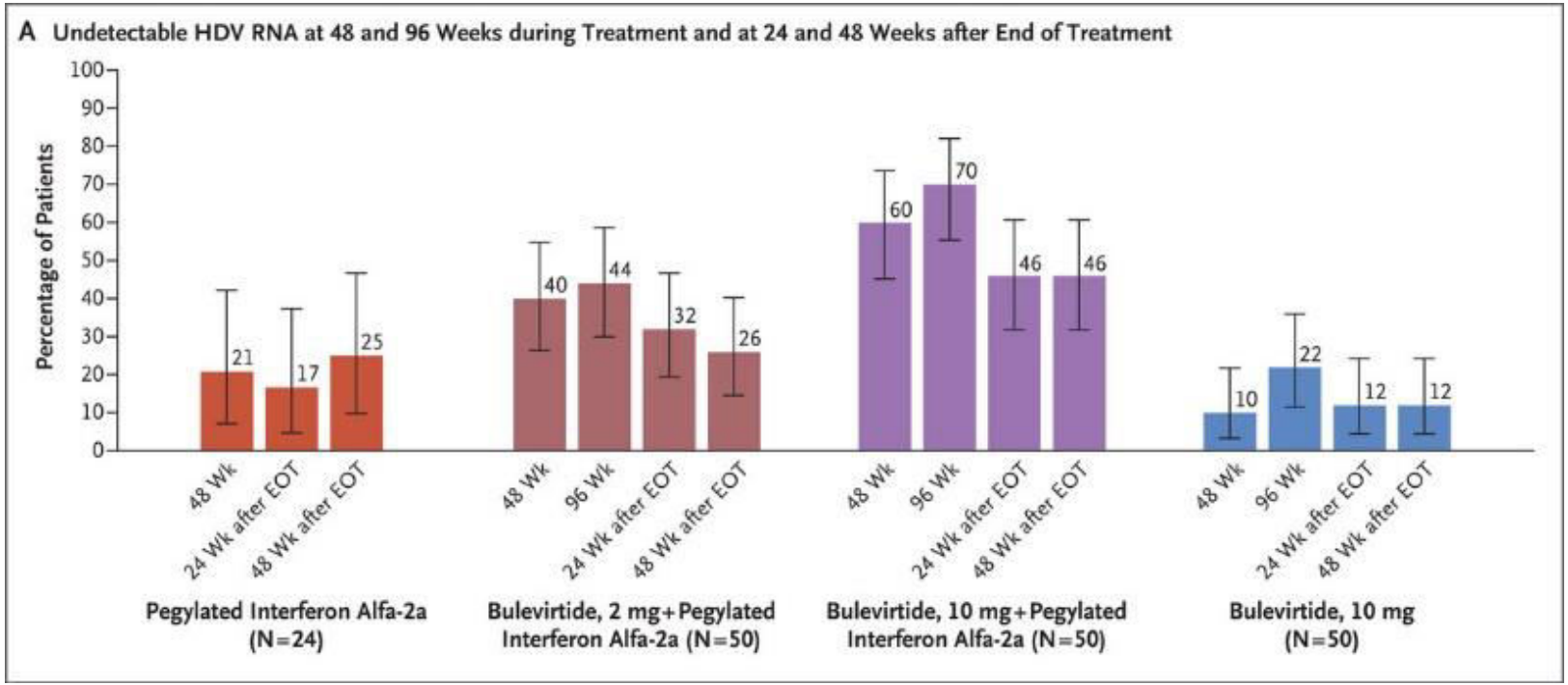
Trial registration: ClinicalTrials.gov number, NCT03852433

Trial funding: Gilead Sciences

Full citation: Asselah T, Chulanov V, Lampertico P, et al. Bulevirtide combined with pegylated interferon for chronic hepatitis D. N Engl J Med 2024;391:133-43. DOI: 10.1056/NEJMoa2314134

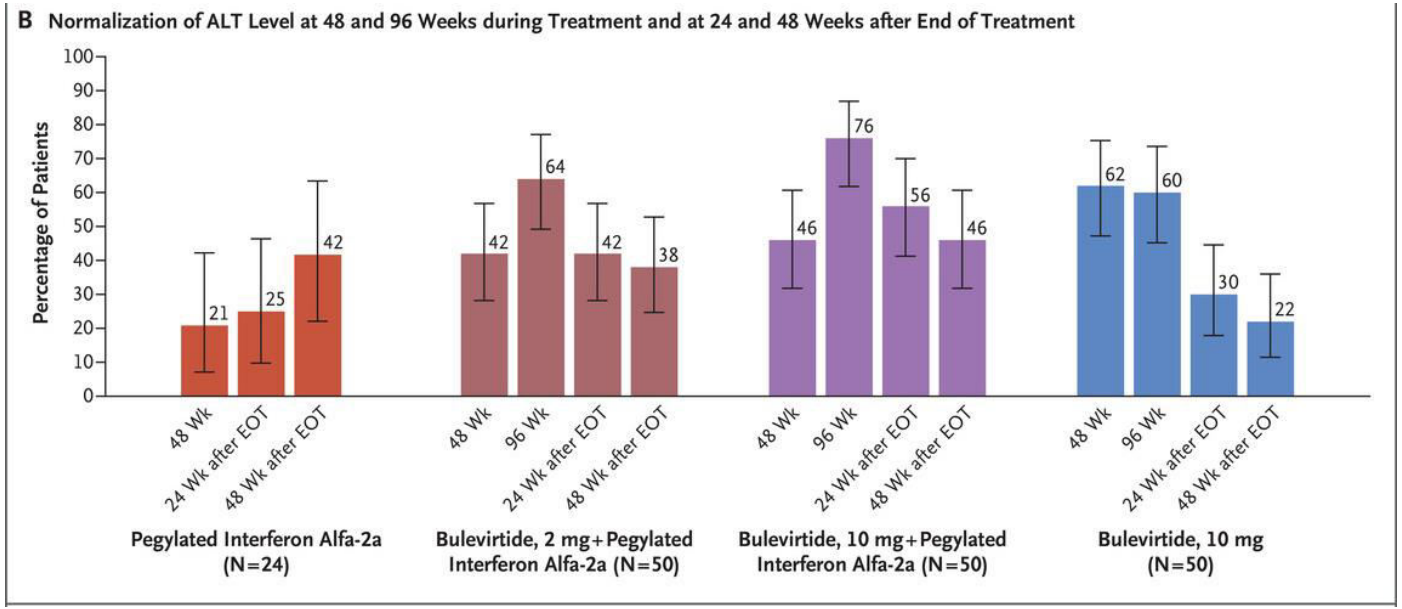
Asselah et al., NEJM 20242024 Jul 11;391(2):133-143.

204 Study: **HDV RNA undetectable**



Asselah et al., NEJM 20242024 Jul 11;391(2):133-143.

204 Study: **ALT normal**



Asselah et al., NEJM 20242024 Jul 11;391(2):133-143.

Bulevirtide 204 study:

Histology

Roulot et al.,

Improvements in Fibrosis and Necroinflammation With Bulevirtide Combined With Pegylated Interferon for Chronic Hepatitis Delta

Delta Cure 2024, Poster 42

Bulevirtide 204 study:

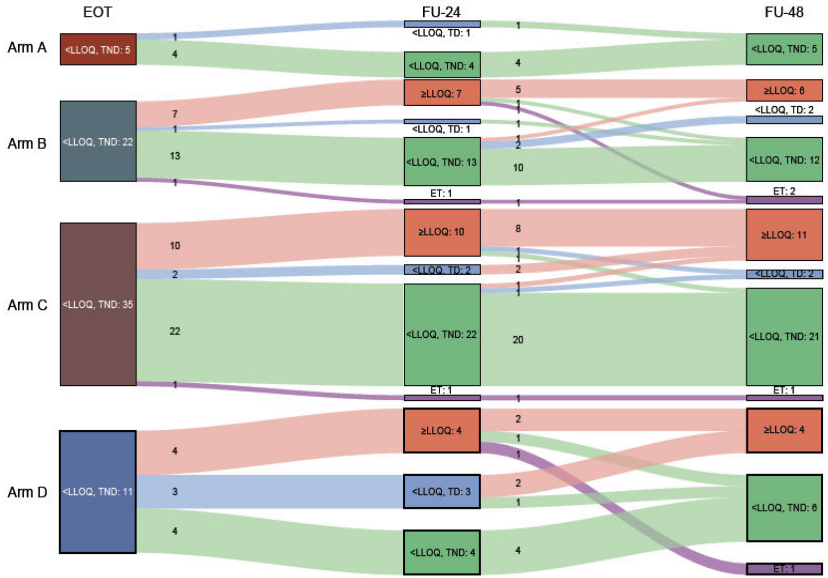
HBsAg

HBsAg loss				
At wk 24 after EOT — no. (%)	0	4 (8)	2 (4)	0
At wk 48 after EOT — no. (%)	0	5 (10)	2 (4)	1 (2)

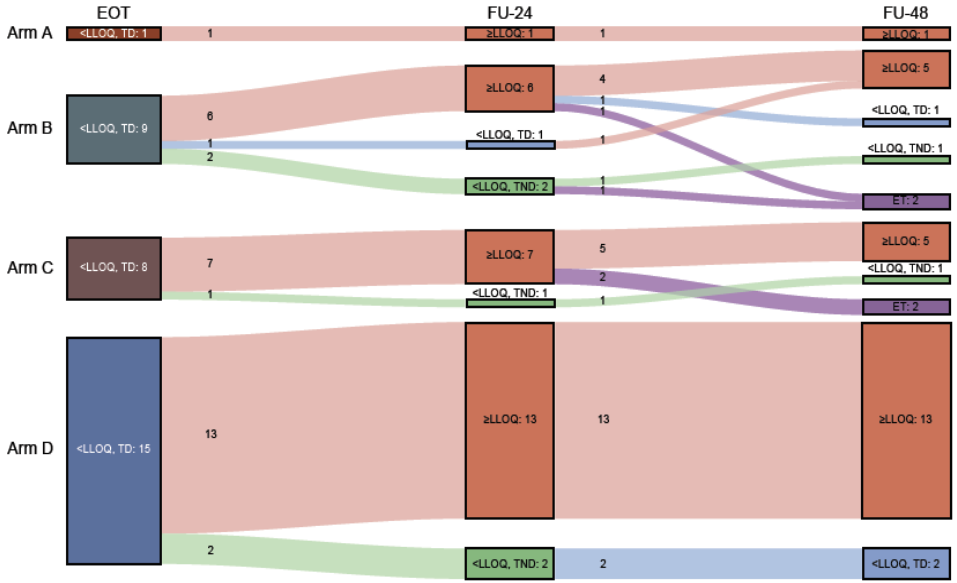
Bulevirtide 204 study:

Risk of relapse and end-of-treatment HDV RNA

EOT HDV RNA target not detected



EOT HDV RNA <LLOQ but target detected

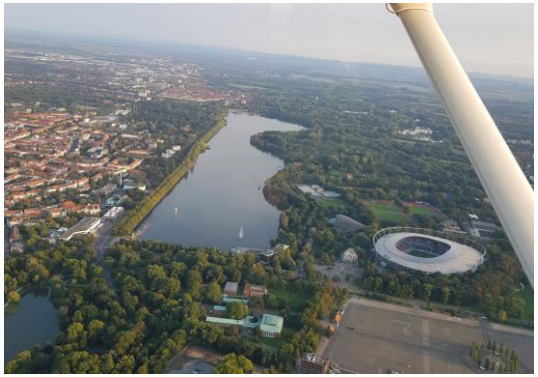


Zoulim et al., Delta Cure 2024 Poster 40

Bulevirtide for Hepatitis D: The “MYR”-Trials

- **202** n=118 24 weeks
  Proof of concept, HDV relapse was not associated with severe flares
- **203** n=90 48 weeks
  IFN combination synergistic effects, HBs decline with low doses of BLV!
- **204** n=175 96 weeks
  10mg in combination clearly superior, off treatment response possible!
- **301** n=150 96-144 weeks
  continued response in the far majority of patients with clinical improvement

4th DeltaCure Meeting: Hannover October 9/10 2025

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